REVIEW OF THE U.S. ENVIRONMENTAL PROTECTION AGENCY'S TOBACCO AND SMOKE STUDY

HEARING

BEFORE THE

SUBCOMMITTEE ON SPECIALTY CROPS
AND NATURAL RESOURCES

OF THE

COMMITTEE ON AGRICULTURE
HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

FIRST SESSION

JULY 21, 1993

Serial No. 103–26

Printed for the use of the Committee on Agriculture

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REVIEW OF THE U.S. ENVIRONMENTAL PROTECTION AGENCY'S TOBACCO AND SMOKE STUDY

WEDNESDAY, JULY 21, 1993

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON SPECIALTY CROPS
AND NATURAL RESOURCES,
COMMITTEE ON AGRICULTURE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:25 a.m., in room 1300, Longworth House Office Building, Hon. Charlie Rose (chairman of the subcommittee) presiding.

Present: Representatives Baesler, Bishop, Condit, Inslee, Pomeroy, English, Peterson, Volkmer, Lewis, Kingston, Goodlatte, and Dickey.

Also present: Representative E (Kika) de la Garza, chairman of the committee, and Representative Barlow, a member of the committee.

Staff present: Jan Rovecamp, clerk; Keith Pitts, Joan Teague Rose, James A. Davis, John Riley, and Stacy Steinitz.

OPENING STATEMENT OF HON. CHARLIE ROSE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NORTH CAROLINA

Mr. ROSE. Good morning, everyone. I have convened this subcommittee today to consider a number of important scientific questions that are raised by the recent report from the EPA on environmental tobacco smoke or ETS.

As you know, this report has received considerable attention since its release in January of this year. Some, including some in Congress, have claimed that the report's conclusions justify legislation to restrict smoking in workplaces, restaurants, public buildings, and elsewhere. Others have questioned the report's scientific basis.

These critics contend that EPA's conclusions about the health effects of ETS are unsound, that the Agency manipulated the statistics, ignored relevant data that disagreed with its conclusions, and flouted its own guidelines. In their view, EPA has sacrificed science to serve predetermined policy goals.

These are serious charges, but I think that we are justified in approaching the EPA report with considerable skepticism. This is not the first time that questions have been raised about the Agency's scientific competence. Indeed, former Administrator Reilly was

aware of the problem and sought to address it by commissioning a panel of outside experts to review EPA's handling of scientific issues. The report issued by this panel in 1992, entitled "Safeguarding the Future: Credible Science, Credible Decisions," was highly critical of the Agency.

The panel found that currently EPA science is of uneven quality and the Agency's policies and regulations are frequently perceived as lacking in strong foundation. In addition, the panel admonished EPA that "science should never be adjusted to fit policy, either consciously or unconsciously."

We will hear today from EPA officials responsible for the ETS report. I want to see whether they can give common sense answers, in terms comprehensible to us and the general public, to the criticisms that have been made of their work. We also will hear from a number of scientists from outside the Agency who have analyzed the relevant literature. I am sure that their expertise will be most helpful to us.

Taking our cue from the expert panel's report, I hope that by the end of the day we will find out whether EPA's ETS risk assessment report is based on "sound science" or whether the data or ETS has been "adjusted to fit policy." This is a necessary exercise before any policy decisions based on the report can be regarded as "credible decisions" that really will safeguard the future.

Mr. Lewis, do you have an opening statement?

Mr. LEWIS. No, sir. I have no opening statement.

Mr. ROSE. Do other members of the panel have an opening statement? Also, any statements submitted by the members will appear at this point in the record.

Mr. BARLOW. I have a statement I would like to submit for the record.

Mr. ROSE. Without objection, so ordered.

[The prepared statements of Mrs. Clayton and Mr. Barlow follow:]

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Congress of the United States
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OPENING STATEMENT FOR REP. EVA M. CLAYTON SUBCOMMITTEE ON SPECIALTY CROPS AND NATURAL RESOURCES

HEARING ON ENVIRONMENTAL TOBACCO SMOKE 21 JULY 1993

Thank you Mr. Chairman. I appreciate you holding this hearing on a very significant issue relating to the conclusions of the finalized draft of the Environmental Protection Agency's report on Environmental Tobacco Smoke. I am hopeful that this hearing will be helpful to the subcommittee in understanding the issues and methodology relating to this EPA study. In the final analysis, I believe that it is crucial to the tobacco industry that we hold this hearing. Mr. Chairman, I follow your lead in protecting North Carolina's farmers. Your experience and commitment to North Carolina's tobacco

farmers speaks louder than words.

My First District of North Carolina has more flue-cured tobacco than any congressional district in the nation. In the state of North Carolina, tobacco production comprises over 20 percent of total farm product. It is a cornerstone of our rural based economy. I am hopeful that we can continue to protect our farmers' livelihoods through fair policies. While I am mindful of the studies which are released from the scientific community, I am concerned about the methodology employed in yielding conclusions. In this context, I am aware of the various reactions to the EPA study and the actions which have been taken by various Members of Congress.

Again, thank you Mr. Chairman for holding this hearing. I hope that the Subcommittee can derive a broader understanding of this issue through today's proceedings. Finally, I would like to welcome the panelists to the Subcommittee.

Thank you.

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July 21, 1993

Statement by U.S. Rep. Tom Barlow
Specialty Crops and Natural Resources Subcommittee

Mr. Chairman, I want to commend you for holding these hearings.

The announcement by the Environmental Protection Agency that it had determined that environmental tobacco smoke is a direct cause of cancer and is responsible for 3,000 deaths a year is an extremely weighty charge.

In fulfilling its responsibilities, EPA has a responsibility in all cases to make a very careful scientific evaluation scrupulously following guidelines established and accepted by the scientific community.

Instead, we find in this instance, EPA departed from its own guidelines and principles generally followed and practiced in epidemiological science in order to reach what certainly appears to be a predetermined conclusion.

The federal government must not on fault-ridden grounds attack or damage a crop and industry as important to Kentucky, North Carolina and other states as tobacco. When smoking is limited without carefully weighed scientific reasoning we aren't just asking the fellow down the hall to go outside for a smoke, we are asking tens of thousands of farmers to find a new way to make a living, and doing so on the basis of EPA prejudice, not EPA scientific wisdom.

Just like the apple growers in Washington and all the other producers who use and need fertilizer, pesticides and herbicides, the tobacco growers in the Southeast are entitled to fair treatment. The extent to which substances pose an environmental risk or threat to human health should be very carefully evaluated based on research carried out using established and accepted scientific principles.

If EPA and other federal agencies are going to make predetermined policy and then manipulate science to support that policy, not only tobacco but the whole of agriculture, the American economy and the American people are in deep trouble.

Thank you, Mr. Chairman.

Mr. ROSE. Our first panel is Dr. William H. Farland, Director of the Office of Health and Environmental Assessment, Office of Research and Development, Environmental Protection Agency.

He is accompanied by Dr. Steven Bayard, the Project Manager for ETS Risk Assessment, Office of Health and Environmental Assessment, Office of Research and Development, Environmental Protection Agency, Washington, DC; Dr. Hugh McKinnon, Director of the Human Health Assessment Group, Office of Health and Environmental Assessment, Office of Research and Development, Environmental Protection Agency, Washington DC.

I want to thank you for being here.

There were others from your Agency that we had hoped would be with us. Mr. Waxman changed the date of his hearing from tomorrow until today and was able to take several of our witnesses away from us.

But we will do the best we can in no way diminishing your abilities and your statements.

We thank you for being here.

Dr. Farland.

STATEMENT OF WILLIAM H. FARLAND, DIRECTOR, OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT, OFFICE OF RESEARCH AND DEVELOPMENT, U.S. ENVIRONMENTAL PROTECTION AGENCY, ACCOMPANIED BY STEVEN BAYARD, PROJECT MANAGER FOR ETS RISK ASSESSMENT, AND HUGH W. McKINNON, M.D., DIRECTOR, HUMAN HEALTH ASSESSMENT GROUP

Mr. FARLAND. Good morning, Mr. Chairman and members of the subcommittee. Thank you for the opportunity to appear before you today to discuss scientific and procedural issues regarding EPA's report on passive smoking.

As you mentioned, I am accompanied today by Dr. Steven Bayard, a biostatistician in our Human Health Assessment Group, who is the Project Manager, and one of the primary authors of the report.

I also have with me Dr. Hugh McKinnon, a public health physician who is Director of our Human Health Assessment Group.

As you are aware, the U.S. Environmental Protection Agency published an assessment of the respiratory health risks of passive smoking in January of this year. The document has been prepared under the authority granted to the EPA Administrator, including title IV of the Superfund Amendments and Reauthorization Act of 1986—Radon Gas and Indoor Air Quality Research—which directs EPA to conduct research and disseminate information on all aspects of indoor air quality.

The report which was reviewed extensively by scientists from outside of the EPA concludes that exposure to environmental tobacco smoke or ETS, commonly known as secondhand smoke, is responsible for approximately 3,000 lung cancer deaths each year in nonsmoking adults in the United States and seriously affects the respiratory health of hundreds of thousands of children. My written testimony summarizes the development of the report, the scientific review process, the major findings, and the scientific approach. The

testimony concludes with some responses to several tobacco industry criticisms of the report.

In recent years, comparative risk studies performed by EPA and its Science Advisory Board have consistently ranked indoor air pollution among the top five environmental risks to public health. As part of its efforts to address all types of indoor air pollution, EPA's Indoor Air Division in 1988 requested the EPA's Office of Research and Development to undertake an assessment of the respiratory health effects of passive smoking.

Because of both resource and time limitations, the assessment was limited to respiratory health effects, both cancer and noncancer. The report was prepared by my office, the Office of Health and Environmental Assessment within the Office of Research and Development, and was written by both in-house staff and outside contracting assistance.

Before being released in draft form for public review, the passive smoking report received many internal reviews, mostly from within the Office of Research and Development. Various parts of it were also reviewed by selected outside experts, both from other Federal agencies and from academic institutions. Revisions incorporated the reviewers' comments wherever possible.

The first external draft of this assessment was released for public review and comment in June of 1990. In December 1990, EPA's Science Advisory Board, a committee of independent outside scientists, conducted a review of the draft report and submitted its comments to the EPA Administrator in April of 1991.

In its comments, the SAB's Indoor Air Quality/Total Human Exposure Committee concurred with the primary findings of the report, but also made a number of recommendations for strengthening it. Incorporating recommendations from both the public and the Science Advisory Board, a revised draft was transmitted to the board in May of 1992 for a second review. Following a July 1992 meeting, the SAB panel endorsed the report and its conclusions, including a unanimous endorsement of the classification of environmental tobacco smoke as a group A or known human carcinogen.

EPA also received and reviewed public comments on the second draft and integrated all appropriate material into the final risk assessment. The final report was released in January of this year at a joint press conference held by former Administrator Reilly and former Department of Health and Human Services Secretary Sullivan.

Based on the weight of the available scientific evidence, EPA has concluded that widespread exposure to environmental tobacco smoke in the United States presents a serious and substantial public health risk.

In adults, ETS is a human lung carcinogen, responsible for approximately 3,000 lung cancer deaths annually in U.S. nonsmokers. ETS has been classified as a known human carcinogen under EPA's carcinogen assessment guidelines. This classification is reserved for those compounds or mixtures which have the strongest data to determine a cause-and-effect relationship, including data from human populations. Only 10 to 15 other agents, including asbestos and radon, have been classified by EPA as group A carcino-

gens, and ETS is the only one for which cancer has been observed at typical nonoccupational environmental levels.

ETS has subtle but significant effects on the respiratory health of nonsmokers including coughing, phlegm production, chest discomfort, and reduced lung function.

In children, ETS exposure increases the risk of lower respiratory tract infections such as bronchitis and pneumonia. Our estimates are that between 150,000 and 300,000 of these cases annually in infants and young children up to 18 months of age are attributable to exposure to ETS. Of these, between 7,500 and 15,000 are estimated to result in hospitalization.

In addition, ETS exposure increases the prevalence of fluid in the middle ear, a sign of chronic middle ear disease. Fluid in the middle ear is a major cause of hospitalization of young children for an operation in the United States.

ETS exposure in children irritates the upper respiratory tract and is associated with a small but significant reduction in lung function.

In addition, ETS exposure increases the frequency of episodes and severity of symptoms in asthmatic children. The report estimates that 200,000 to 1 million asthmatic children have their condition worsened by exposure to environmental tobacco smoke; and ETS exposure is a risk factor for new cases of asthma in children who have not previously displayed symptoms.

EPA reached its conclusions concerning the potential for ETS to act as a human carcinogen based on an analysis of all available data. Specifically, the finding that EPA should be classified as a group A carcinogen is based on the conclusive evidence of the dose-related lung carcinogenicity of mainstream smoke in active smokers, the chemical similarities of mainstream smoke and the side stream smoke given off the burning end of the cigarette and the known exposure and uptake of ETS at levels which could increase risk.

The finding is bolstered by the statistically significant exposure-related increase in lung cancer in nonsmoking spouses of smokers which is observed in analysis of more than 30 epidemiology studies from eight different countries that examined the association between secondhand smoke and lung cancer. The weight of the evidence analysis for the noncancer respiratory effects in children is based primarily on a review of more than 100 studies, including over 50 recent epidemiology studies of children whose parents smoke.

EPA is not the only Federal agency that has evaluated environmental smoke. The EPA's conclusions on the respiratory effects of passive smoking strengthen and confirm those of earlier assessments by the U.S. Surgeon General in 1986 and the National Research Council of the National Academy of Sciences in 1986. The World Health Organization has also concluded that ETS causes excess risk of lung cancer in 1986 and other respiratory disorders in 1992. The National Institute of Occupational Safety and Health in 1991 concluded that occupational exposure to ETS causes increased risk of lung cancer and probable heart disease.

The position of the National Cancer Institute in 1993 is that ETS is a proven cause of lung cancer in nonsmoking adults and is asso-

ciated with an increased risk of coronary heart disease. Since the cutoff date for literature inclusion in the EPA report, several new studies have been published which provide additional evidence of respiratory effects from ETS exposure. Six of these are particularly relevant, one each on sudden infant death syndrome, SIDS, and asthma, and four on lung cancer.

Three of the recent studies on ETS exposure and lung cancer in nonsmoking women add to the data base of the 30 studies analyzed in the EPA report. Two of these, Stockwell, et al. from the Journal of the National Cancer Institute and Brownson, et al. from the American Journal of Public Health are large U.S. case-control studies which find significant increased risks among nonsmoking women in the highest category of ETS exposure based on the amount their husbands smoke.

Similar results are reported in the very recent study of nonsmoking Chinese women by Liu, et al., in the American Journal of Epidemiology; Liu also found a statistically significant increase in risk in the most exposed group, based on husband's smoking. In addition, Stockwell, et al. found significantly increased risks for high levels of household exposure in children.

I believe it is important that we put these risks associated with ETS in perspective. The EPA estimates that about 20 to 30 percent of all lung cancers caused by factors other than smoking are attributable to environmental tobacco smoke.

Another way of expressing this is that the increased risk of dying from lung cancer is about 1 in 1,000 from all ETS exposures outside the home.

For reference, a one-pack-a-day smoker experiences lung cancer risks approximately 100 times higher or a 1-in-10 risk. Exposure to ETS varies, but higher exposures are associated with higher risk.

For example, people whose spouses smoke in the home face an average increased risk of 2 in 1,000. Estimated risks in this range are considered high. For comparison, EPA generally sets its standards or regulations so that increased cancer risks are below 1 in 10,000 to 1 in 1 million.

In other words, the increased lung cancer risks associated with exposure to environmental tobacco smoke are at least an order of magnitude greater than the cancer risks for virtually any other chemical or agent that EPA regulates.

The additional risks on childhood respiratory health make an even more compelling case for the public health impact of ETS. In my written testimony I have also addressed many of the criticisms of EPA's approach to and findings of this analysis.

We will now be pleased to answer questions from the subcommittee.

[The prepared statement of Mr. Farland appears at the conclusion of the hearing.]

Mr. ROSE. Thank you very much, Dr. Farland.

Could you describe to us EPA's guidelines for carcinogen risk assessment, and in particular, what those guidelines say with regard to the classification of a substance as a group A carcinogen?

Mr. FARLAND. Yes, Mr. Chairman.

The Agency has a long history of documentation of its guidance on carcinogen assessment. It put out its first interim guidance in 1976 and followed with final guidance that we use today in 1986. That particular guidance is used by scientists within the Agency, and by those outside to understand how the information is going to be translated into risk assessments, and to help us with the work that we do in my office.

We use a weight of evidence approach. This particular set of guidance stresses the importance of considering all the information, and it uses a classification scheme as one aspect of the guidance that breaks carcinogens down according to the understanding of the evidence available on them. They are categorized as A, known human carcinogens; B, probable human carcinogens; C, possibly human carcinogens; and then there is a D category, which is not classifiable; and an E category for those chemicals that have been sufficiently well tested and don't show a carcinogen response.

The A carcinogen class is our highest class of evidence. It generally will include human information, epidemiology studies, information on human metabolism, and other types of human data. It will have looked carefully at those epidemiology studies in order to attempt to rule out confounders that might cloud the analysis of those particular studies. This is a classification system that has been broken up into these five categories.

Mr. ROSE. I understand that. You have been over the classification system.

Is it not true that in your guidelines that you indicate that for a substance to be classified as a group A carcinogen there must be sufficient data in humans, that is, epidemiological data?

Mr. FARLAND. The type of information that we are talking about is all of the human data. We are looking for a classification that would include sufficient human data.

Mr. ROSE. You contend that you have sufficient human data?

Mr. FARLAND. We do. That sufficient human data includes information on active smoking in humans, it includes information on the exposure of humans to——

Mr. ROSE. What are some other class A carcinogens?

Mr. FARLAND. The Agency has classified between 10 and 15, radon, benzidine, byschloromethyl ether, vinyl chloride, asbestos, nickel, arsenic—these are chemicals that have reached the categorization of being known human carcinogens.

Mr. ROSE. What are some class B carcinogens?

Mr. FARLAND. Class B carcinogens have an adequate animal data base.

Mr. ROSE. What are they?

Mr. FARLAND. Formaldehyde——

Mr. ROSE. So tobacco smoke is more carcinogenic than formaldehyde?

Mr. FARLAND. It is not a question of more carcinogenic; it is the data base that is available.

Mr. ROSE. Environmental tobacco smoke is A and what was the classification for B?

Mr. FARLAND. That is a probable human carcinogen. Formaldehyde falls into that category and there is limited human evidence on formaldehyde.

Mr. ROSE. It might be poisonous if you drank it, but you are talking about the vapor from it; is that correct?

Mr. FARLAND. Yes. There is limited human evidence that it causes upper respiratory tumors.

Mr. ROSE. How was a determination as to formaldehyde arrived at? Was it done through a comparison of various studies that were done around the world or was there a particular test that you all conducted?

Mr. FARLAND. The formaldehyde conclusion——

Mr. ROSE. You were probably looking at studies that had been done in various places?

Mr. FARLAND. That is right.

Mr. ROSE. Did you apply the 95 percent or the 90 percent confidence level in the case of formaldehyde?

Mr. FARLAND. I would have to go back to look at that. The test for statistical significance in those cases would have been 95 percent.

Mr. ROSE. You applied 90 percent to environmental tobacco smoke which made it a class A carcinogen, but you haven't looked at formaldehyde or other substances at the 90 percent level?

Mr. FARLAND. No. The test for statistical significance is at the 95 percent level in both cases.

Mr. ROSE. What did you change to 90 percent? I am not obviously asking the right questions, Doctor. What did you change from 95 to 90 percent?

Mr. FARLAND. The important issue is that the statistical significance——

Mr. ROSE. What was the level that you changed from 95 to 90 percent in the case of environmental tobacco smoke?

Mr. FARLAND. We used a 95 percent statistical significance test that is one-tailed and resulted in a 90 percent confidence interval. It is a standard statistical procedure. It is the confidence interval that comes from the 95 percent statistical test and is one-tailed.

Mr. ROSE. So you did not use a 90 percent confidence downgrade in your conclusions as to environmental tobacco smoke?

Mr. FARLAND. This is not a downgrade. A 90 percent confidence interval is not a downgrade. A 90 percent confidence interval is consistent with a 95 percent one-tailed test. And that is what we used, a 95 percent one-tailed test of significance to determine whether or not the observed relative risk was significant compared with controls.

Mr. ROSE. All right. I better go back and learn new math. I thought 95 was higher than 90, but I am wrong.

Mr. FARLAND. Mr. Chairman, you are correct that a 95 percent confidence interval is a more stringent statistical test and there are 95 percent statistical significance tests that use a 95 percent confidence interval. But in the case where one has evidence that the effect is likely to be adverse and not beneficial, the statistical use of a one-tailed test is appropriate.

Mr. ROSE. So you assumed it was bad and did a one-tailed test?

Mr. FARLAND. We assumed based on the evidence of lung cancer and smoking that the result would likely be an adverse effect and we used a one-tailed test of significance.

Mr. ROSE. But based on your studies and the way you classified them, you are telling us that the fumes from tobacco smoke are more carcinogenic than the fumes from formaldehydes?

Mr. FARLAND. This is a different——

Mr. ROSE. There are people out there who obviously work for you who are shaking their heads.

Mr. FARLAND. It is not a matter of quantification. It is not a matter of it being more carcinogenic or less carcinogenic; it is the weight of the weight of the evidence that we have available on that substance.

Mr. ROSE. You are really getting my attention.

Mr. FARLAND. A known human carcinogen may not be as potent a carcinogen, as strong a carcinogen, as one that we don't have human data on. There is a difference between hazard and potency.

Mr. ROSE. What does the risk ratio of one mean?

Mr. FARLAND. A risk ratio of one means that there is no increase in relative risk so that this is a ratio of——

Mr. ROSE. Increase?

Mr. FARLAND. No increase in relative risk over a background or a control population.

Mr. ROSE. So a risk ratio of less than one means what?

Mr. FARLAND. A risk ratio of less than one depending on the confidence around the estimate, may mean that it is protective or it may mean that it is equivalent to one.

Mr. ROSE. Above one, what does that mean?

Mr. FARLAND. Again, it means in this case that there would be an increased relative risk or, depending on the confidence, it may be equivalent to one.

Mr. ROSE. Looking at some studies that you have used, association between risk of lung cancer and childhood exposure to tobacco smoke among nonsmoking women, are the risk ratios above or below one?

Mr. BAYARD. Are you talking about childhood exposure?

Mr. ROSE. I just said that. Association between risk of lung cancer and childhood exposure to tobacco smoke among nonsmoking women; the risks are all less than one.

Mr. BAYARD. Did you look at Stockwell or Janerich?

Mr. ROSE. This is the Fontham study.

Mr. BAYARD. That study showed no increase in risk in children. The Stockwell study has shown an increase in risk and the Janerich study showed an increase in risk. In the Fontham study, she discusses at the end that her study did not show an increase, and that conflicted with the Janerich study.

Mr. ROSE. Then you could conclude that according to the Fontham study, you should expose children to tobacco smoke to reduce their risk; is that right?

Mr. BAYARD. Only if you are willing to conclude by the Fontham study that you should definitely not expose people to ETS at work because they showed a very large increase for people exposed at work. The relative risk for exposure as children was very close to one, as I understand it; maybe 0.9-something.

Mr. ROSE. So when you use a one-tailed approach as opposed to a two-tailed approach, you don't look at the upside and the downside; you just assume that there is a danger here?

Mr. BAYARD. You assume that if there is any effect—this is for lung cancer—we did it different than for lung cancer than we did in noncancer respiratory effects. For lung cancer, we had evidence that high levels of tobacco smoke caused lung cancer and that is pretty good evidence, about 9 million people studied worldwide; and most people will admit that tobacco smoking causes lung cancer.

So we believe that with the lower levels of tobacco smoke from environmental tobacco smoke there would not be a protective effect, but if there were any effect, it would be an adverse effect. So we only used a one-tailed test or 90 percent confidence intervals for the analysis of ETS epidemiology and lung cancer. But for the childhood respiratory effects, we used 95 percent confidence intervals because we didn't have the evidence from smoking in children causing noncancer respiratory effects; so we did do it two ways in the same report.

Mr. ROSE. I kind of broke a committee rule here. I should hear the whole panel. I have asked basically 1½ questions. Are you the only one going to give a statement, Dr. Farland?

Mr. FARLAND. Yes, Mr. Chairman.

Mr. ROSE. Then I am not wrong. Could you explain what criteria the Agency uses when evaluating epidemiological studies to determine whether an association could be due to chance?

Mr. FARLAND. The Agency uses an approach that was published by Bradford Hill. It is a traditional approach that goes through a number of criteria for causality, and it includes a number of things like consistency of the data, the number of studies, the strength of the response, the biological plausibility and those sorts of issues. In addition to that, we use statistical approaches as well as those general approaches for evaluating causality.

Mr. ROSE. Would you describe as sufficient any single epidemiologic study or the combination of a series of such studies that reports a relative risk that is statistically not significant? Would you describe as sufficient any single epidemiologic study or the combination of a series of such studies that reports a relative risk that is statistically not significant?

Mr. FARLAND. Mr. Chairman, the only example that I can think of where we have argued a strong case for known human carcinogenicity where the epidemiology data base may not be statistically significant is vinyl chloride where there is a very limited number of cases, but there are very specific types of cancers so the cause and effect relationship based on the biological arguments is very strong.

Mr. ROSE. Dr. Farland, at the Science Advisory Board review of ETS risk assessment in July 1992, you stated that ETS risk assessment has been an innovative approach and that it bears some merit in terms of future approaches for risk assessment. Does that mean that in the future EPA will place undue emphasis on the much criticized statistical technique of meta-analysis?

Does the Agency have guidelines on the use of meta-analysis? And moreover, if the ETS risk assessment is to be a template for future directions, does it mean that the Agency intends to override existing carcinogen risk assessment guidelines in favor of a less strict weight of evidence approach that would leave the Agency much more freedom to interpret data as it might wish?

Mr. FARLAND. I am not sure that I got all those questions.

Mr. ROSE. At the Science Advisory Board's review of the risk assessment on July 1992, you stated that ETS assessment has been an innovative approach, that it bears some merit in terms of future approaches for risk assessment.

One, does that mean that in the future you will place emphasis on the much-criticized statistical technique of meta-analysis? Two, does the Agency have guidelines on the use of meta-analysis; and three, if environmental tobacco smoke risk assessment is to be a template for future directions, does it mean that the Agency intends to override existing carcinogen risk assessment guidelines in favor of a less strict weight of the evidence approach that would leave the Agency much more freedom to interpret data as it might wish?

Mr. FARLAND. Thank you for repeating.

I made a statement about the innovative approaches that we use. I think this is a unique data base where one has 30 lung cancer studies and over 100 studies in children. Fortunately, we don't have many cases where we have that much human data on an environmental contaminant.

With regard to your question on the emphasis on meta-analysis, the use of meta-analysis depends on the quantity and quality of the studies that you have available, whether they can be combined, and there will be few cases where we will have enough information, sufficient data, sufficient numbers of studies of similar design and so on to be able to use meta-analysis. We are committed to use this particular approach which is gaining favor within the epidemiologic and statistical community in future cases where it would fit.

In terms of guidelines for meta-analysis, the Agency has none, but it does very carefully lay out the process it used for meta-analysis and subjects it to external peer review as part of its peer review process. In addition, we are working with industry and academic groups to hold a workshop on meta-analysis in this upcoming year to look at some of the principles that would be included in a general guidance document on meta-analysis.

In terms of the cancer guidelines, we are in the process of revising our cancer guidelines to move along with the evolution of the scientific data. We will focus on weight of the evidence approaches and will continue to focus on a strong scientific judgment component within our guidance.

Mr. ROSE. Is there any substance for which EPA has used a set of epidemiologic studies pertaining to a substance other than the one under study, even though perhaps similar in some respects, in order to determine a group A classification?

Is there any substance that you have used a set of studies pertaining to a substance other than ETS, even though perhaps similar in some respects, in order to determine a group A classification?

The answer is no, isn't it, Doctor?

Mr. FARLAND. I think the best example that we have of that is the case of our evaluation of benzidine containing dyes. In that particular case, benzidine is known to be a human carcinogen. Dyes that contain benzidine that are likely to be metabolized, and have been in some cases shown to be metabolized by humans so that benzidine appears in the urine, are considered as known human

carcinogens where there is no direct epidemiologic data on those dyes. In that case, we use the surrogate data from benzidine and the epidemiology studies there to make conclusions on these other dyes.

Mr. ROSE. The EPA risk assessment on environmental tobacco smoke determined that ETS could be classified as a group A carcinogen solely on the basis of comparisons with the epidemiology of active smoking. This is at odds with the recommendations of EPA's Science Advisory Board.

Could you explain why in this instance EPA decided to reject the advice of the Science Advisory Board?

Mr. FARLAND. Let me comment and perhaps Dr. Bayard would like to add an additional comment. My understanding was that the Science Advisory Board suggested to us that although we had spent a lot of time evaluating the epidemiology studies, that it was possible to make a conclusion simply on the similarities between active and passive smoking.

They didn't suggest that we should do that instead of evaluating the epidemiology studies; they just said that the strongest case would be based on both of those and that we should go back and improve the arguments on the correlation with active smoking in addition to our analysis of epidemiology studies.

Mr. BAYARD. The statement you are referring to I think was made by Dr. Lippman at the second Science Advisory Board meeting July 22, 1992. That statement, as a lot of statements made at that meeting, did not get into the Science Advisory Board report to us on November 20, 1992, so that oral statement did not represent the Science Advisory Board's consensus.

Our conclusion was that we could label environmental tobacco smoke a known human carcinogen based on the similarity of environmental tobacco smoke to mainstream smoke, with both containing the same carcinogen, and the known lung cancer response from mainstream smoke down to very low doses with no evidence of a threshold. This conclusion was in the draft which we sent to the SAB for review, and to which that report of November 20 referred.

So our conclusions were in the second draft which went to the Science Advisory Board for review. They agreed with the conclusions in their November 20 report to us, and it remained in our final report which was published in December.

Mr. ROSE. I have a lot more questions for Dr. Farland, and for Dr. Bayard, but in fairness to the members of the panel, I am going to yield to Mr. Lewis for questions and then to my colleagues on my right and then Mr. Lewis, whoever he will wish to recognize. Mr. Lewis.

Mr. LEWIS. Thank you, Mr. Chairman.

Dr. Farland, Dr. Shapiro of the Sloan Epidemiological Unit stated in a paper that the use of meta-analysis and observational research should be abandoned and the guidelines also go on to state that negative results from a well-designed and well-conducted study that contains usable exposure data can be used to define the upper limits of risk. What implications does this have for a series of studies where several of the larger studies report no increase in risk?

Mr. FARLAND. As I mentioned there is controversy with regard to the use of meta-analysis, but it is growing in favor in terms of trying to combine studies to increase their power to evaluate effects. There are individuals in the scientific community who are not comfortable with the use of meta-analysis and feel that perhaps it should not be used.

There are others who have used it extensively to evaluate carcinogens. A report by Sir Richard Doll, for instance, used meta-analysis extensively and suggests that it is the best way to evaluate a particular class of compounds that he is looking at. The implications of the meta-analysis approach is that one can combine studies showing an effect, that have an increased relative risk, with those that could not show an effect and get some sort of a sense as to the contribution of that no effect finding on the overall estimates of relative risk.

There is a rationale for doing that sort of thing, and there is a basis for, rather than focusing only on the positive studies, using the positive and nonpositive studies, the no relative risk increase studies, in trying to reach your conclusions. That is what meta-analysis helps us to do.

Mr. LEWIS. One of the largest studies by Brownson reports no increase in risk. This should have a significant implication for the risk assessment, is that true?

Mr. BAYARD. The Brownson study is 1 of 33 studies on lung cancer and environmental tobacco smoke among never-smoking women. The Brownson study found a significant risk among the women most heavily exposed. If you take all the women, the women who were ever exposed versus those never exposed to their husband's smoke, the Brownson study found no overall increase in risk.

You have to understand that these epidemiology studies done at true environmental levels are not the easiest studies to detect any kind of an effect. In fact when EPA calls something a known human carcinogen, most often the studies are based on high occupational levels, anywhere from 100 to 1,000 times what a typical environmental level will be. ETS is the only agent which EPA has ever found to be, ever declared, a known human carcinogen, which has actually been found to be carcinogenic at true environmental levels.

Getting back to the Brownson study, Brownson concluded that ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking. Two other studies which have also appeared since our cutoff date for literature review have also found statistically significant increases at the highest level and one found a significant dose response trend.

The question is would Brownson have changed our results? The answer is no. That would have been 1 of 33 epidemiology studies on ETS and lung cancer, but there are tons of other studies that also went into our weight of evidence, hundreds and hundreds of other studies. The answer is no.

Mr. LEWIS. Is there any other substance for which EPA has used a set of epidemiology studies pertaining to the substance other than the one under study even though perhaps similar in order to determine a group A classification?

Mr. BAYARD. Nickel causes lung cancer and nasal cancer in pyrometalurgical refinery workers. Those people are exposed to high doses of nickel which also probably contains sulfuric acid, so we have found that, yes, some of these nickel salts are carcinogenic.

But do we know if it is ever going to cause lung cancer at typical environmental levels? We don't know that. We have never seen—with the exception of environmental smoke—cancers from our group A carcinogens, at typical environmental levels that we know about. Asbestos, we have never seen cancer from background levels in schools. We know we spend a lot of money to clean them up, but we have really never seen cancer at these levels in schools.

We hypothesize that that is going to be the case based on modeling but that is not true for environmental tobacco smoke. So nickel is one. Coke ovens is one. Coke oven workers who have high exposure to coke oven emissions come down with lung cancers. By the time these emissions have dissipated and get into the ambient environment we don't particularly know if they are actually going to cause lung cancer.

Does that answer your question?

Mr. LEWIS. I think it does because I really don't know what you used. It was my understanding you only used environmental tobacco smoke. Apparently you are telling the subcommittee that you did use others for comparison.

Mr. BAYARD. The question you asked was whether there were any other chemicals for which we used like studies, I thought that meant, in which the studies that we used were actually different from what was available in the environment.

My response was that, yes, with both nickel and coke ovens we had occupational exposures which are probably going to be somewhat different from what the environmental exposures would be; not only in dose, but in physical chemical characteristics.

Mr. FARLAND. Mr. Lewis, I also mentioned to the chairman the idea that in the case of some of the benzidine containing dyes, we had used epidemiology studies from benzidine in order to classify those specific dyes. That would be another case where we have used surrogate data.

Mr. LEWIS. After EPA's adjustment to the 90 percent confidence interval, how many of the studies reported statistically significant increase in risk?

Mr. FARLAND. Could I use the chart that we had up here? That would be helpful.

Mr. LEWIS. Fine.

Mr. FARLAND. This chart basically just shows the weight of evidence approach that we used. There were 30 epidemiologic studies of ETS and lung cancer.

If you compared the 30 studies for ever versus never exposed, which is the lowest level of evaluation, of the 30 studies, 24 showed an increased relative risk, 9 were statistically significant. That is a finding that would not likely be due to chance.

The probability of getting 9 statistically significant studies among 30 by chance is a 1 in 10,000 probability. When we broke that group of 30 down into the 17 studies which characterized exposure and used that exposure level and looked at the increased

risk in the highest exposure level, 17 out of 17 studies showed an increased relative risk, 9 were statistically significant in that group and that is a probable finding of 1 in 10 million.

We wanted to see which studies showed a positive dose trend. Of the 14 studies that showed the characteristics to evaluate dose response, 10 were statistically significant. By chance, about 1 in 1 billion that you would get 10 out of 14 coming up as a probability of occurrence by chance.

Mr. LEWIS. Could I stop you there for a moment and ask you, in the first instance you said nine were statistically significant?

Mr. FARLAND. Correct.

Mr. LEWIS. In the second, 9; and in the third, 10. That was 9 out of 24 or 30, and 9 out of 17 studies and 10 out of 14. How about the rest?

Mr. FARLAND. The others were studies of lesser power, smaller studies. They showed a nonstatistically significant increase or no increase at all. That could be due to the nature of the study. It could be a true evaluation of that particular test, or it could be due to chance that those results showed no increase.

Mr. LEWIS. Wouldn't those studies be significant to bias these nine in some way?

Mr. FARLAND. They continued to raise uncertainty within the overall assessment because not all studies have shown a positive response, but not all studies are equal. They are not designed the same way, looking at the same populations——

Mr. LEWIS. You can design a study to be the way you want it.

Mr. FARLAND. I would agree that that could be done. I would hope that it would not be done.

Mr. LEWIS. At the 95 percent confidence level, Doctor, how many of the United States' ETS epidemiological studies of spousal smoke exposure to lung cancer report significant results as employed in this risk assessment?

You did mention this in your opening statement, but at the 95 percent confidence level, how many?

Mr. BAYARD. May I answer that?

For the ever versus never exposed, I think there was only one or two, Fontham or Fontham and Chorea. Only 1 or 2 out of the 11 showed overall statistical significance. When you start looking—you would have only expected out of 20, if there is no effect, remember we talked about the 5 percent significance level.

When you deal with a 5 percent significance level, if there is no effect, it would be significant 1 time of 20. If no effect, we would have expected 0.5 of the 11 studies or less than one study to be statistically significant.

Of the ever versus never exposed, there were one or two U.S. studies which were statistically significant. When you start looking at trends, two or three were statistically significant and in the highest exposure groups, three were, but a lot of studies just didn't have the information available to test at the highest exposure groups. So based on the 11 studies, we didn't see a tremendous effect in the United States and we explained that by looking at all different countries and our analysis separated the results by the different countries.

Mr. LEWIS. Didn't you find that those studies at the 95 percent confidence level did not meet the criteria that you are telling me until it was dropped down to 90?

Mr. BAYARD. No. That isn't the way I remember it. You are talking about only the 11 U.S. studies?

Mr. LEWIS. Yes.

Mr. BAYARD. It doesn't matter whether there were two studies, if there were two significant studies at the 95 percent level or one or two with the one-tail test. I don't think there was much of a difference because even at the 95 percent level, there wasn't that much significance; if you did the ever versus never, which is a crude measure. A better measure to take is the highest exposure group.

Don't forget, everyone is exposed to ETS. If you take ever versus never, even the people you say are never exposed will be exposed, so you are comparing risks of those with a little bit more exposure to those with a little less exposure. It is hard to define a result from any one study. That is why we tried to take all possible studies, the positive and the negative studies, and tried to see what the story was.

Mr. LEWIS. I understand as scientists you have to defend your studies.

Mr. BAYARD. They are not my studies. We just did the analysis.

Mr. LEWIS. I have a problem as the chairman did, going from 95 to 90, it seems like it was establishing a statistical modality in order to meet a study requirement. I am not accusing you of that, but it is confusing to me.

Mr. BAYARD. We did it two different ways in the same report. For the childhood respiratory effects, we used a two-tailed test, for the lung cancer analysis we used a one-tailed test based on the prior evidence that active smoking causes lung cancer. So we did it two different ways.

Mr. LEWIS. Mr. Chairman, I have one last question for Dr. Bayard. You stated at an open meeting in EPA on January 7, 1993, chaired by Mr. Bretthauer, that the use of 90 percent confidence intervals was justified because you had a prior feeling that ETS would cause cancer and so it was appropriate to use a so-called one-tailed test and look only at increased risk.

How often has EPA adjusted its statistical standards on the basis of a prior feeling?

Mr. BAYARD. We do use 90 percent confidence intervals when we extrapolate from high animal to low human exposure, so in that sense yes, we do use 90 percent confidence intervals. The question of whether we adjusted these intervals to get the desired results, it is just the way we did it. We looked—before we even looked at the data, we said what is our prior belief on environmental tobacco smoke; is it going to be beneficial or adverse? Do we have enough evidence to say it is not going to be beneficial? If you don't know which kind of effect you are going to have, you use a two-tailed test.

If you have a strong enough belief that any effect you have is going to be adverse, you use a one-tailed test and that is exactly what we did. My belief is that any effect of environmental tobacco smoke would be an adverse one for lung cancer.

That is not true for childhood respiratory effects. We didn't have that prior belief. This is standard statistical procedure. It was something we raised to our Science Advisory Board. We did not change the methodology. We used a one-tailed test in the first draft, we used a one-tailed test in the second draft, we used a one-tailed test in the final, for lung cancer. We used a two-tailed test in the first draft for respiratory effects, we used two tailed in the second draft for respiratory effects and we used two tailed in the final. We did not change it. We brought it before the SAB and they examined it and said it is fine. It is standard statistical procedure. You learn it in your first course in statistics.

Mr. LEWIS. Mr. Chairman, I didn't want to confuse anything.

Mr. ROSE. Mr. Baesler.

Mr. BAESLER. From your last statement, Doctor, you did start this study with the feeling that you felt there was a problem?

Mr. BAYARD. No.

Mr. BAESLER. You just said that.

Mr. BAYARD. When I started in 1988 I didn't know anything about——

Mr. BAESLER. The previous answer to his question you said that you did a one-tailed test because you had the prior feeling that, first of all, there wasn't anything positive out of tobacco smoke, it was going to be negative, and therefore you did the one-tailed test and you had a prior feeling that there was going to be a problem.

Mr. BAYARD. With respect to lung cancer?

Mr. BAESLER. Yes.

Mr. BAYARD. We felt if there was an effect——

Mr. BAESLER. You said you had a prior feeling that the effect would be negative. You didn't say if there was an effect.

Mr. BAYARD. If there were an effect of environmental tobacco smoke we did not expect it to be protective——

Mr. BAESLER. You are backing up. Nowhere did you put if there was effect. The answer to his question was you had a prior feeling there was going to be a negative effect. That is the way you just answered the question.

I think that is a big difference to suggest that if there was an effect. The critics will say that you never went into this, EPA never went into this study with the question if there is an effect. The critics will say you went into the study, there will be an effect, how do we substantiate it? Is that true or not true? When you started the study, you had a prior feeling there would be a negative effect; therefore. Therefore you wanted to use a one-tailed effect—mumbo jumbo, nobody understands, though you have said a great deal, and I don't. Representing the largest burley industry in the country, it concerns me that assumptions that you make so cavalierly you make that can so negatively affect such a large industry, which this feeling that you had when you started this bothers me.

You said we had this feeling that there was going to be a negative effect; therefore, we did this one-tailed study, which for whatever scienctic reason, we went from 90 percent to 95 and nobody understands it, unless it is another scientist. We did that, nothing wrong with that.

You answered the question about in 1992 some person questioned on the panel about well, are we doing it right or not and you

cavalierly threw that off, that wasn't the consensus of the panel, that was one fellow and we didn't use it until the next two times.

We have cavalierly thrown off every dissenting view and that bothers me. I have no idea what you are talking about, haven't understood a thing you said all day other than the fact you are trying to defend a study that basically attacks a large industry and you started with the presumption that it would be negative. That bothers me, because you are supposed to represent all of us, not just one side.

The second concern is you said a minute ago in answer to a question, something about animals. Am I wrong or right? I have no idea, but do you often in these type of studies, class A, use animal-type testing? You do, don't you?

Mr. BAYARD. We look at all the evidence.

Mr. BAESLER. Did you in this one?

Mr. BAYARD. Yes. We looked at animal evidence.

Mr. BAESLER. With respect to smoke?

Mr. BAYARD. Yes.

Mr. BAESLER. So you did that the same as you do the others; correct?

Mr. BAYARD. We looked at animal evidence; yes.

Mr. BAESLER. How did it affect the animals?

Mr. BAYARD. It is more mutagenic than mainstream smoke when applied to the mouse skin and in cell colony tests.

Mr. BAESLER. Maybe it is not possible, but can you just—I think basically maybe I am dumb, but I don't understand a thing you are saying. Maybe that is intentional. Tell us in common terms that somebody will understand what we are talking about. We are not scientists.

Mr. ROSE. What does mutagenic mean?

Mr. BAYARD. Causes gene changes in the DNA which is thought to be a mechanism related to the start-up of cancer.

Mr. BAESLER. We talked about 11 studies that you had used in your approach to this analysis. The meta-analysis, you used 11 studies.

Mr. BAYARD. No. We used 30 epidemiology studies in the meta-analysis.

Mr. BAESLER. Did you combine 11 studies into one big study, or is that wrong?

Mr. BAYARD. That is correct. We used 30 studies and when you use a meta-analysis you decide whether or not the studies are different between countries—the results are different between countries. We found that we had eight countries which broke into six country groupings.

There were 11 United States studies and 5 from Japan and 4 from China, Greece, the United Kingdom, and Sweden. We found that the results differed between countries.

Mr. BAESLER. The 11 U.S. studies, that is where the term 11 comes from?

Mr. BAYARD. That is correct.

Mr. BAESLER. How many of those studies had concluded there wasn't a problem, of the 11?

Mr. BAYARD. Out of the 11, probably none, but let me tell you how. Out of those 11, 8 showed increased risk. Between one and

three was statistically significant, depending on how you count them.

One showed a slightly decreased risk. That was Janerich, which found a highly significant increased risk for childhood exposure. I am trying to remember the two that actually showed decreased risk, and I don't remember offhand.

Mr. BAESLER. Eight of the studies showed increased risk and you said according to how you view it, it could be a problem?

Mr. BAYARD. I am sorry, I missed the question. I don't understand you.

Mr. BAESLER. Not necessarily one to three. I thought you had a statement about according to how you view it could have been a problem.

Mr. BAYARD. Eight showed increased risks for the ever versus never exposed. One of those was statistically significant for the ever versus never exposed.

Mr. BAESLER. One of the eight?

Mr. BAYARD. That is correct. Another two were statistically significant if you looked at dose response trends or the high exposure groups.

Mr. BAESLER. Let me ask a simple question. You individually, did you think there was a problem when you started?

Mr. BAYARD. No. I didn't think that at all. I started in 1988. I didn't know what an RSP was.

Mr. BAESLER. You said you started in 1988——

Mr. BAYARD. I first was introduced to this problem in 1988. All I do is risk assessment for a living. That is my job. This is just another pretty face. I do these things. I don't belong to any program office. We are a group that does this for a living. That is my training.

So my answer was no, when I first started I didn't believe it at all. It was only when I saw the evidence on dose response trends and the epidemiology studies that I couldn't explain any other way.

Mr. BAESLER. Thank you.

Mr. ROSE. Mr. Goodlatte from Virginia.

Mr. GOODLATTE. I am concerned about how this environmental tobacco smoke policy guide was developed. Can you—Dr. Farland, can you enlighten me on that?

Mr. FARLAND. Mr. Goodlatte, the policy guide is a product of the Office of Air and Radiation, not of our Office of Research and Development. We had no involvement in the policy guide other than to make sure that they didn't somehow change the science that was being provided to them through our report.

Mr. GOODLATTE. So you don't know how they contracted for the development of that guide?

Mr. FARLAND. That was not within our purview.

Mr. GOODLATTE. Is there anybody here with you today that——

Mr. FARLAND. They are in the other hearing.

Mr. GOODLATTE. Maybe I need to go to the other hearing.

Mr. BAYARD. You could have invited them over.

Mr. GOODLATTE. Let me go back to this 95 percent confidence level versus 90 percent confidence level, Dr. Bayard, do you understand the implications of this study?

Tell me what you understand are the public implications of the study that you put out here?

Mr. BAYARD. Of the EPA study?

Mr. GOODLATTE. Yes.

Mr. BAYARD. It hasn't been helpful to me.

Mr. GOODLATTE. I am talking about the enormity of this; not just talking about the effect on a major industry, but the implications and considerations every person has to take into account based upon this report that you presented. This is an enormous consideration, what your association is with others in the workplace, your homes, your children, and so on.

Mr. BAYARD. Much more than I ever thought it would be.

Mr. GOODLATTE. Under those circumstances, do you think it is appropriate to use a lower standard to measure the tests than you use ordinarily in epidemiological studies?

Mr. BAYARD. Let me turn that around and say if I am testing at true environmental levels where everyone is exposed, do I want to be 95 percent certain that something causes cancer or am I happy to be 90 percent certain?

Mr. GOODLATTE. I don't think that is the measure here. The measure here is the number of tests that you can throw out at the 95 percent level as compared to the 90 percent level.

Mr. BAYARD. If the question is what is the difference in significance tests as between the one-tailed and the two-tailed——

Mr. GOODLATTE. Here we have what could be one of the most important studies that you have ever participated in, and one of the most important considerations that this panel will consider regarding the danger of something to society, and you step down to a lower level of confidence, and I don't understand why you do that. The Washington Post on June 23, quoted EPA as saying that the unquestionable link between smoking and lung cancer makes it defensible to accept a lower standard of proof in the case of ETS. Now, we don't accept that kind of lower standard in other measures of determining culpability in our society.

We don't say that if somebody is guilty of one murder and it is proved beyond a reasonable doubt that we can accept a lower standard, that we can accept a lower standard of significantly likely because they have already been convicted of one murder if the other murder is unrelated to that—we don't accept that in terms of scientific possibility, saying the first poll showed that x was likely to be the opinion, so we will accept a lower standard now. Since we are doing it again, and the first one turned out that way we expect the second will turn out that way.

Mr. BAYARD. Do you willingly expose yourself to asbestos because it happens to cause cancer in workers exposed somewhere around 100 times what you might get from a little dose?

Mr. GOODLATTE. The studies conducted should be accepted. When there are other studies out there that countervail that, why would you apply a lower standard?

Mr. BAYARD. There were 30 studies out there and we tried to include them all. I think that is something that we did that hasn't been done as much in the past. In the past EPA reports have focused more on the positive studies. We tried to focus more on the negative studies.

Mr. ROSE. Mr. Bishop.

Mr. BISHOP. Thank you very much, Mr. Chairman.

The release of this risk assessment of environmental tobacco smoke has really been harshly criticized by a number of independent scientists. I have a serious concern with reports that the Agency staff may have ignored the universally accepted standards of scientific evidence in order to justify its position. So I really want to focus on the scientific review process to make sure that we have a scientific determination here rather than just a policy review to rubber stamp a preconceived idea.

I would like to ask a few questions and maybe get some responses. There have been some allegations that the Science Advisory Board panel that reviewed the risk assessment was comprised of a number of individuals that had conflicts of interest and that they had obvious biases against smoking.

There are also allegations that some of them had actually been involved in preparing the document that they were asked to review. Also there were allegations that a number of well-funded recipients of EPA grants were included in the Science Advisory Board panel that conducted the review.

Also, there are allegations that the EPA staff had engaged in behind-the-scenes maneuvering in order to stack the panel in favor of the Agency's position. I don't know whether that is true or not, but if those kinds of Agency allegations are out there, I think it is incumbent, particularly with the tremendous ramifications of these findings, or these alleged findings, on the environment throughout our country, and not to say what the ramifications will be on the tobacco industry, which is a very important economic contributor, I just think that we need to look at the science of it.

Let me just ask you a couple of specific questions.

One, did members of the EPA Science Advisory Board assist in the development of your findings in the risk assessment report, yes or no?

Mr. BAYARD. Mainly based on their comments at public reviews, with one exception that I can think of. On my first draft in 1990, before we released it for public review, we asked one fellow who subsequently became a member of the Science Advisory Board for his comments, David Burns from the University of California, San Diego, and he provided comments. David Burns had been the senior editor in many of the Surgeon General's reports, including the 1986 report. So I asked for his comments. He gave me a lot of comments and subsequently became a member of the SAB.

I actually recommended that he was suitable to review our report.

Dr. BISHOP. Do you see a conflict of interest on having an advisory board of scientists reviewing a report which they contributed to the findings of?

Mr. BAYARD. He was 1 of 18 members of the SAB. I recommended Nathan Mantel a consultant to the Tobacco Institute, Dr. Gross—no not Gross—Joseph Fleiss, who is a well-known biostatistician. All these people had been recommended to me by the Tobacco Institute.

Dr. Kabot, I recommended, who had been recommended by the Tobacco Institute and Dr. Kabot and Dr. Burns were chosen. Those were the only two people that I recommended who were chosen.

Mr. BISHOP. It is my understanding that there was a policy or an understanding established that if the data and the EPA's scientific guidelines did not show that ETS was a carcinogen, then the Science Advisory Board felt that the guidelines should be revised. Is that accurate?

Mr. FARLAND. Mr. Bishop, maybe I can address that point. The chairman of the Science Advisory Board took a question at the end of one of the public meetings about the sufficiency of the data for environmental tobacco smoke and the question was whether or not according to EPA's guidelines this could be classified as a class A carcinogen. His response was with this amount of information, if it could not be classified as a class A carcinogen, then the guidelines would have to be changed. That is, if the guidelines were getting in the way of the classification of this as a class A carcinogen because they were somehow restrictive to certain types of data, and wouldn't allow you to use all the information available, then there would need to be a change.

That was not a SAB finding. It was a comment of the chairman to a question of him. It specifically points to the fact that the guidelines where not restrictive, that they are meant to be used with scientific judgment and to weigh all of the evidence available.

Mr. BISHOP. The draft report of April of 1991, page 29, "If the guidelines for carcinogenic risk assessment can be used to cast doubt on a finding and inhalation of tobacco smoke by humans causes an increased risk of lung cancer, the situation suggests a need to revise the guidelines."

Now, I really am not in a position to determine whether there is a risk of harm that is created or not. My concern is with the effect of what you are doing here and the effect of this EPA study on our country that we ought to really be looking at a scientific process and that we ought to be acting on and be driven by science and not by a policy and trying to come on the back end and justify a policy that has been predetermined.

This is just a lack of objectivity. It suggests a subjective approach here, to change the rules to fit what you expect—what you want the outcome to be. That concerns me because of the effect that what you are doing could have on my district.

Mr. FARLAND. Mr. Bishop, I would like to try and convince you that this study was extensively reviewed by our scientific peers. We took a lot of comment and responded to those comments in terms of the development of this report. The Science Advisory Board selection of members was done in an open process, as is always done.

I can't comment personally on the selection of those individuals since that is outside of my jurisdiction, but as Dr. Bayard mentioned we did submit a series of names that were scientists who were well-qualified and had represented a number of sides of this particular issue. The question about the guidance that is put out there is clearly one that is an argument for the use of scientific judgment and not for allowing a strict framework in which one eliminates information so as not to consider it when you reach your conclusions. This is not looking at an issue of trying to change the

approach in order to fit the end. This is a strong endorsement of using good science, using good scientific judgment, and this is something that both we and our Science Advisory Board are committed to.

Mr. BISHOP. I appreciate the statement you are making, but it does not seem consistent with what has been brought out today and what I have seen. It seems to me that there is more of a cloud here than there is clarity. Based upon the process, it seems to me the integrity of the story of the study has certainly come into question. Based upon the objectivity of the contributors or the lack of objectivity, it seems there is more of a cloud than clarity.

Mr. BAYARD. Did you know we are criticized more by the antismoking folks for the makeup of the Science Advisory Board? Did you know Dr. Lippman was attacked because he was chairman of the committee for indoor air research [CIAR], which is heavily funded by the Tobacco Institute.

Did you know Dr. Woods was in the process of negotiating a $1.2 million grant with the Tobacco Institute at that time? In fact, 6 of the 17 members had financial ties to the Tobacco Institute. We were heavily criticized by the antitobacco folks.

Mr. BISHOP. It seems like what you are saying is you are agreeing more of a fog has been created? I don't think what you need is to have——

Mr. FARLAND. I think what we are seeing is these are individuals with strong scientific credentials, and that is not an issue with regard to where their funding is coming from in terms of their ability to reach conclusions on this particular report. We were criticized from both sides because of the makeup of this report. It was a balanced report and very strongly scientifically staffed.

Mr. BISHOP. I appreciate your comments. I am not certain that I have any more clarity now that I did before you started answering.

Thanks a lot.

Mr. ROSE. I told Mr. Lewis I was going to call on Mr. Barlow next, then our colleague here and then over here.

Mr. Barlow.

Mr. BARLOW. Doctors, thank you very much for being here. I have not had a chance to go through all your studies. I assume they will be in the record.

I wonder if you might help me. You all obviously saw these and prayed over them for a long time.

Mr. FARLAND. Once or twice.

Mr. BARLOW. Give me help here, basic down-to-earth help and guidance, if you can. How many of these studies would you estimate deal with physical dimensions of the areas in which environmental tobacco smoke arises? In other words, to give you an example: Environmental tobacco smoke in a room the size of this may not be as omnipresent as the same amount of tobacco smoke in a closet might be. Can you give me an estimate on the numbers of studies that cover that?

Mr. FARLAND. The 30 epidemiology studies we looked at were based on exposure of nonsmoking women, spouses of smokers in their home; so that the exposure to tobacco smoke in the home was

considered to be the exposure under test in these epidemiology studies.

Mr. BARLOW. Now somebody smoking over in the far corner of that room, of this room here—which is a very large room, for the record—may not have any impact on me sitting up here on the opposite side of the room. Would you agree?

Mr. FARLAND. The smoke will be diluted as it goes up into the room; that is correct.

Mr. BARLOW. May not even reach this side of the room, depending upon the drafts and so forth?

Mr. FARLAND. It is possible; that is right.

Mr. BARLOW. Are variations such as that taken into account?

Mr. FARLAND. Again, the way this was done was to look specifically at spouses of smokers; and in that particular case, as Dr. Bayard mentioned, these are very difficult epidemiology studies because we all have some exposure to environmental tobacco smoke, so we were looking for groups of people, or the investigators were looking for groups of people, who had a higher than normal exposure to environmental tobacco smoke—still environmental levels but a higher than normal average exposure—so that they could determine whether an effect was produced. That is what all 30 of these studies tried to look at, smoking in the home.

Mr. BARLOW. It is difficult to construct a case when you have an extreme variation in physical surroundings; you would agree, right?

Frequency of smoke, it is very difficult again to make a statistical—one statistical finding based on many variations and frequency of smoke. If someone were to smoke a cigar in the back of this very large room, it might not have any impact upon me; especially if I am only coming in once a week, twice a week, and that person may be only smoking a cigar once or twice a week.

Mr. BAYARD. Not only that, but for lung cancer you have to figure out what the exposure has been over the past 30 years.

Mr. BARLOW. You have a very difficult job coming up with a statistical sample.

Mr. BAYARD. It is hard to believe any of these studies a priori would show an effect.

Mr. FARLAND. I think that is an important point with regard to the chart we showed. The first approach I showed, analyzing the 30 studies, was a question of "ever" versus "never." It was just simply whether or not you lived in a home with a smoker. There are vast differences in those types of studies.

Mr. BARLOW. Wouldn't you say it might be unfair to tobacco farmers and the tobacco industry to make a one-phrase condemnation which—environmental tobacco smoke is kind of becoming a pejorative phrase, a negative phrase—when you have many variations and conditions over many years? Wouldn't you say that might be unfair?

Mr. FARLAND. Again, I think the point we are making is that from a scientific and a public health perspective, we can talk about the hazards, about the risks; but people have to make their own judgments, and risk managers in local situations, in States, in restaurants, have to reach conclusions with regard to how that risk is going to be managed.

This is not a general condemnation in the sense that a small amount of environmental tobacco smoke will cause all of these effects we are talking about. This is a discussion about real people who have experienced effects. That has been measured in scientific studies, both in lung cancer and in childhood respiratory effects.

People have to take that information and make informed risk management judgments, whether personal judgments or whether or not they are some sort of regulatory judgments at the State, local, or Federal level.

Mr. BARLOW. You are making a judgment applying one short phrase, environmental tobacco smoke, which, as I say and many people feel, has gotten to have a negative implication, connotation on the worse case situations. You are classifying the heavy smoke in a very confined space like a closet, equating that with very infrequent smoke in a room as large as this?

Mr. FARLAND. In terms of a hazard call, it is equivalent to talking about asbestos as a carcinogen based upon occupational exposures. It is based upon talking about other types of occupational exposures to chromium, or other types of metals or benzidine dyes or any of those in terms of a hazard. There is a hazard to exposure to environmental tobacco smoke.

Now, the risks depend upon the exposure. If you can avoid environmental exposure, or if you can lessen your exposure to environmental tobacco smoke, you are going to lessen your risk.

Mr. BARLOW. Some of those hazards may be very minimal, right?

Mr. FARLAND. Under certain conditions, absolutely.

Mr. BARLOW. I can recall in my lifetime my father would smoke an occasional pipe or cigar. I enjoyed as a young child smelling the smoke as it wafted across the room; and any hazard I might have incurred in that process might have more than been made up for the love of being with my father and enjoying his enjoyment of his pastime, true?

Mr. FARLAND. Mr. Barlow, that is a personal choice. I think it is absolutely true. I think you ought to be informed about the potential hazards and then make that judgment.

Mr. BARLOW. Thank you, Mr. Chairman.

Mr. ROSE. Thank you. But the data would suggest that what you just described would be good for you.

Mr. BARLOW. Yes.

Mr. ROSE. Mr. Lewis.

Mr. LEWIS. Mr. Kingston of Georgia.

Mr. KINGSTON. Thank you, Mr. Chairman and Mr. Lewis. I wanted to ask you about the integrity of the study, which I know you are getting pounded on a lot.

I hate to be redundant; but my father was a college professor. He told me years ago when, unfortunately, Federal dollars got involved on university campuses, all the studies suddenly became politically correct, with the conclusion meaning that more money had to be spent on that particular item that they were studying. In other words, it was predestined, whatever their conclusion was going to be.

Knowing the pressures you folks are under, do you feel in your heart of hearts that this study was objective and just—I am not trying to belabor. Just a simple yes.

Then, since you are shaking your heads—yes, all three of you agree with that—another thing that we studied—I studied chemistry in college. Whenever you do a study, you have to look at the prejudice of the scientist. With that in mind, do you folks smoke? Do any of the people in the study smoke?

Or was it—maybe a little bit, as Mr. Bishop suggested, maybe there was some antismoking sentiment in the scientists, that was there. Is that the case? Do you think—did you have a mixture? That is very important to know what the prejudice of the scientist is.

Mr. BAYARD. I think probably it is better I answer that. If you want Dr. Farland to——

Mr. KINGSTON. No. I know you are the point man.

Mr. BAYARD. I am the project manager for this. I had something to do with choosing the contracting support. In terms of money, my paycheck just doesn't change. It hasn't changed for 14 years other than cost-of-living allowances. I have never been offered money from the antitobacco folks or the tobacco folks. I don't know what that means.

In terms of smoking, I smoke an occasional cigar or occasionally smoke a cigar—good ones, actually.

In terms of the objective, a couple of my—I have five children. Four are adult children. Two smoke, two don't. My exwife smokes, but I don't blame smoking for her.

In terms of objectives, this is what I do for a living. In terms of getting people, now, what I tried to do was get people—the most unbiased people, people who knew nothing about tobacco smoke because it had been——

Mr. KINGSTON. The reason I am concerned about that, as a new Member of Congress, I find almost whatever you are trying to find out about, if it comes from one party, it goes this way; if it comes from another party, it goes that way. It is not tobacco studies but budget, anything you ask.

In fact, I don't know if you have seen the article—I will be happy to share it with you—a book called Galileo's Revision: Junk Science in the Courtroom. In it, Peter Huber of the Manhattan Institute for Policy Research talked about how lawyers get scientists in a courtroom, that come up with conclusions that basically back up their argument.

I just see a real corruption in the pure art of science these days. It really depends on who is writing the check for the grant, the study.

I say that because the National Cancer Institute had done a very comprehensive study which they released in November that said there was no significant link; and, I don't know if this is—if we are getting politics in the lab. That worries me.

Mr. BAYARD. I can tell you I am not antismoker. I don't get paid any more for what I say. No matter what I say today, I will get paid the same tomorrow. I get paid every other Tuesday.

You are going to get some other contractors coming up here. You ask them if they will get paid tomorrow depending upon what they say.

I stand by my own personal objectivity. I am sure if I had had any links, they would have been discovered by now; you would have known about them.

Mr. FARLAND. To follow up on that, I think it is important we understand the process used for this report. We had numerous scientists involved in reviewing the drafts, as it was developed. Certainly, within our own Office of Research and Development, there was a lot of internal peer review, scientific peers who had no particular biases or no particular connection with this report as they made their views known.

The external scientists that we go to routinely—we go to a wide range of scientists. As Dr. Bayard mentioned earlier, there were some 18 scientists on the Science Advisory Board panel. I mentioned in my opening remarks, in my testimony, that these were follow-up reports to the U.S. Surgeon General's report in 1986, the National Research Council, Academy of Sciences in 1986; the World Health Organization in 1986 and 1992; National Institute of Environmental Health Sciences in 1991; and the National Cancer Institute in 1993.

To suggest that all of those individuals would somehow be biased in a way that would argue wrongly that there is a public health impact of environmental tobacco smoke, I just don't believe it is possible.

Mr. KINGSTON. I am glad to hear that. Let me ask one other question that gets to Congressman Barlow's question. In terms of the size of a room or whatever, when somebody is smoking and the smoke becomes diffused, I suppose the smoke chemically reacts with some other chemical in the air, that the smoke intermingles with oxygen or whatever is out there.

In your study, did you study the effect of a household in the inner city, for example, or maybe one that never uses air-conditioning, compare those two, versus one that is outside with a good breeze? Did you weigh out differences like that?

Mr. FARLAND. Again, these studies are from eight countries around the world. Some of them were actually looking at the use of smoky coal from a heating source. In fact, there appeared to be lung cancer associated with the use of that smoky coal as an indoor air pollutant.

Mr. KINGSTON. Would that skew the study?

Mr. FARLAND. In that particular case, it quite likely wiped out any small effect associated with environmental tobacco smoke.

Mr. KINGSTON. You would eliminate that household from the study?

Mr. FARLAND. In that particular study, the study was actually of a group of individuals who lived under those kinds of conditions. It looked at a number of different ways of evaluating lung cancer; and in that particular study, there was no indication of environmental tobacco smoke or tobacco use causing an increased risk. There was an association with the smoky coal.

Mr. KINGSTON. Would you do the same or did those studies do the same thing if there was radon in the air or somebody living underneath an el train and somebody—in an inner city versus somebody living in suburbia.

Mr. FARLAND. This is why it is difficult using one study to reach conclusions. This is why we had to use all the information available to us. I think what it shows is some studies were much more powerful than others. That some showed no increase may very well have been because both the exposed and the control individuals were showing some lung cancer risk from some other source; and because it pushed both of them up, it washed out the effect of the smoking.

We just do not know. That is the nature of these studies.

Again, this is a fairly unique data base because these are results that are being looked at at environmental levels as opposed to very high levels in the workplace, or what have you.

Mr. KINGSTON. In the 90 versus 95 percent, would that tie into that at all?

Mr. FARLAND. Again, I really believe that the issue of 90 versus 95 percent is a red herring. It is a statistical test of significance that is a 95 percent test. It has a confidence interval of 90 percent; and that 90 percent, as we have agreed to here, is less than 95 percent.

But if the results that one finds are significant at 90 percent, and not significant at 95 percent, in light of all of the biological information, in light of all of the other studies that have been done on animals and other groups like that, you are not going to be convinced by that simple statistic. You are going to make a decision on the basis of biological plausibility, on the basis of consistency of results, of findings from other studies and so on.

That is very important.

Mr. KINGSTON. Thank you, Mr. Chairman.

Mr. ROSE. Thank you very much.

Any further questions?

Mr. Inslee.

Mr. INSLEE. Thank you, Mr. Chairman.

As far as ETS, I am trying to get a grasp of what you are saying. It has been very educational. But is this a situation where you assume that ETS has carcinogenic properties, so the real question becomes, is there enough exposure in real life to produce carcinogenic effects? Do you see what I am driving at?

In other words, is that the real heart of this study?

Mr. FARLAND. Mr. Inslee, you asked the right question: First of all, is there a hazard, a carcinogenic hazard, associated with ETS? The answer to that was brought up in the first discussion.

We categorize it as a category A known human carcinogen. We are quite confident. The question of risk has to do with how much exposure we get.

Now, it is—for chemical carcinogens where there is a substantial data base on mechanisms of action, we can generally assume that there is a linear response from high doses to low doses, so that the probability of a cancer response will decrease as the exposure decreases.

At some point, we are going to reach a level where that probability of cancer risk is no longer significant. It may still be there. There may still be a very small cancer risk associated with it; but given our lifestyle, everything else we do, it will not be significant.

That is what we really have to take into account as we make risk management decisions. Are we dealing with a situation that is high enough to be of concern to us, or are we dealing with occasional exposures that are not necessarily going to be a risk?

What we are telling you in this particular case is that in individuals who lived with smokers we were able to measure—our investigators were able to measure an increased cancer risk using a very crude tool which is an epidemiology study. So it is quite likely that the significance of that cancer risk is sufficient to be a public health concern.

Mr. INSLEE. The report, at least my brief scan of it, indicated there were not workplace studies, that we do not have good epidemiological studies on workplace environments. Is that accurate?

Mr. FARLAND. We did not focus on the workplace environments. I will let Dr. Bayard explain why. We actually talked about that in our report, so it was clear why we used these other studies.

Mr. INSLEE. I think I can assume the reason why. You had lesser levels of exposure, not as much stability in the exposure, those reasons.

But does that indicate that in our public policy we should not use this study for workplace policymaking questions?

Mr. BAYARD. That would be for my response. The fact that a workplace is a much tougher place to look at exposure of environmental tobacco smoke doesn't mean that—I am sorry. To me, if environmental tobacco smoke is carcinogenic in the home, because you are exposed in the home and because you can measure it better in the home means you should be careful in the workplace, too.

In fact, in the numbers in our report we look at both home and nonhome exposures and calculate a total number of potential cancer cases from home and nonhome exposures.

Mr. INSLEE. That is included in the number, then?

Mr. FARLAND. That is right.

Mr. INSLEE. As far as peer review, has this study undergone or should it undergo a peer review process that, customarily, the study would be exposed to?

Mr. FARLAND. This study has undergone as much or more than studies that we have been doing over the past 8 to 10 years.

Mr. INSLEE. As far as this was just an academic study that, as I understand the process, will commonly go through peer review process, has this gone through a similar process?

In other words, do you have a study coming out in a journal?

Mr. BAYARD. We do a few articles for journals. There are usually two or three reviewers. This one had 18, plus all the public review.

Mr. FARLAND. This one was extensively peer reviewed.

Mr. INSLEE. Thank you.

Mr. ROSE. We have been 2 hours on this. We have had our first witness. So we will be here until midnight.

Dr. Farland, in March of 1990, you sent an internal review draft of the ETS risk assessment to various groups within EPA, including the Environmental Criteria and Assessment Office in Cincinnati. What is the role of this office and what type of expertise does it have?

May I suggest an answer for you, and you tell me if I am right or wrong. If you want to add to it, tell me, and you can.

Is it not true the Cincinnati ECAO group is a team of scientists with complementary expertise that involves itself in health risk assessments? The group includes experts in epidemiology and toxicology?

Mr. FARLAND. Yes, Mr. Chairman.

Mr. ROSE. Would you add to that?

Mr. FARLAND. I would say, yes. That is part of my group. That is my Cincinnati office.

Mr. ROSE. I have seen from the documents that you provided to us that in a letter to you from Dr. Sonic from—which one is that; all right—dated April 27, 1990, signed by Acting Director, Dr. DeRosa, the Cincinnati group questioned the use of meta-analysis to support the classification as a group A carcinogen and suggested that the epidemiologic studies more appropriately reflect limited evidence of human carcinogenity.

They also stated that there are substantial differences between mainstream smoke and sidestream smoke, or ETS, and consequently it is difficult to generalize about the properties of one study from the other.

The group also commented that, finally, there are tremendous scientific regulatory and political ramifications of categorizing a substance as a group A carcinogen. With all due respect to the epidemiologists who produced the report, given the inherent limitations of the data and the comparative novelty of the approach used to interpret the data, I would recommend that this approach not be used as the basis of a group A classification.

Now, none of the documents that you provided to us contained any response to these comments, either by you or by Dr. Bayard.

What response did you give the Cincinnati group? Here is the document, technical manuscript review form, recommendations, acceptable after major revision. OK?

Mr. FARLAND. Yes, Mr. Chairman. That was the first draft. As I said, it went through extensive internal review. This is our group.

My response to that was to have a conference call to follow up with the scientists who were involved in the Cincinnati review and with our own scientists here to discuss the data, to discuss the issues they had laid out in that memo; and we took to heart their perspectives on that. They are certainly not the only ones that have provided that type of a perspective.

And we indicated that we would further strengthen the document as we went through the draft, taking other comments into account; and we would supply it to the Science Advisory Board to help us finalize it.

So, again, I think it points out that there is a diversity of views on these particular issues, those within our own group. But we did very strongly address many of the issues that were raised simply because that is the purpose of peer review, trying to understand where the misconceptions or the changes might be.

Mr. ROSE. All right.

On March 9, 1992, you sent a memorandum to several EPA groups asking for a second internal review of a revised draft, I guess that would be the second draft of the risk assessment. How long was the draft document at this time and can you tell us how many weeks were allowed for this review of your second draft?

My indication is that the document was between 300 to 600 pages long, and you gave them about 13 to 14 days to review it.

Mr. FARLAND. That is not unusual, Mr. Chairman, when we are dealing with the second draft of a document. About 2 weeks is what I would have said, although I do not really know that for sure.

Mr. ROSE. Let me move on to my real question here.

I gather the Environmental Criteria Assessment Group in Cincinnati was critical of the time allowed for the review. It so indicates?

Mr. FARLAND. That is also not unusual.

Mr. ROSE. I understand. Dr. Harvey, Director of the ECAO in Cincinnati at that time, wrote on March 24, 1992 in this document that "No one liked the 11-day time allotted for review." He continued, "I suggest that the document manager consider more time for evaluation to balance the seriousness of this document as applied to the public health and the intrinsic value of doing it right on this key health topic."

What was your response to this criticism? Do you think it appropriate to allow 11 days for the thorough review of a 600-page—you already said that is typical. What was your response to Dr. Harvey's——

Mr. FARLAND. Again, Dr. Harvey is my director out there at ECAO; we did talk about that. This is certainly not the only document we worked on. We work on lots of different things. We put time pressures on our scientific staff to review these.

This document was 4 years in the making. It went through a tremendous amount of peer review. While we may not have gotten the extensive commentary from Dr. Harvey's group, we feel it was adequately peer reviewed.

Mr. ROSE. Now, you told us after this April 27, 1990, first draft, you had a conference telephone call, and you took things that they said into consideration; so here comes the—their review of the second draft which, as you observed, they had 11 days to look at and gave it—sent it out on March 24, 1992, almost 2 years later.

The ECAO group in Cincinnati seemed highly critical of this redraft of the risk assessment, as it existed in March 1992. While Dr. Murphy appealed for more time, she did in her limited review find plenty to criticize about the risk assessment. She wrote, "Was there any attempt made to include nonpublished studies which are likely to have nonpositive findings in the review?" She concluded later, "I feel that the importance of the trend test and its associated probability value is overstated. Misclassification and measurement error can mask a dose response trend, but can also sometimes create one."

Moreover, she wrote, concerning the lack of consistency of the histologic-type of lung cancer that, "I feel that it distracts from the presumed causal relationship of lung cancer and ETS."

Here again, we have no copies of your response to that. What was your response to these concerns?

Mr. FARLAND. Again, these comments, along with the other comments from the other groups, were passed on to Dr. Bayard as the manager. He had the opportunity to address those comments. I can let Dr. Bayard speak to that directly.

Mr. ROSE. Make a note, Dr. Bayard. We will come back to you.

Let me just get one more thing out here. Then I am about through.

Dr. Harvey also wrote in his March 24 letter to Linda Bailey-Becht, "I suggest a full discussion of carcinogen category A versus B based on the absence of definitive data of passive ETS in humans. Like it or not, EPA should live within its own categorization framework or clearly explain why we chose not to do so."

Dr. Harvey also wrote that "ECAO–CIN will be most happy to spend further time improving the quality of this document."

What was your response to these criticisms that the Agency's guidelines were not being followed? Did you have discussions on these matters with either Dr. Harvey or his staff? How was this matter resolved?

Mr. FARLAND. I did have discussions with Dr. Harvey on that particular issue, because Dr. Harvey had been with us for a little over a year at that time. He had not been involved in the development of the guidelines, and the discussion about how EPA's classification system was dealing with various types of chemical cases was not particularly well known to him.

We talked about the category A classification. We talked about efforts that were going on to revise our guidelines and to use a narrative-type of approach rather than an alphanumeric classification, a box.

Mr. ROSE. Could you provide for the record any correspondence or notes you had on this subject, please?

Mr. FARLAND. Mr. Chairman, I will look. I don't believe I have any notes on that. I think they would have been sent up before if they were available.

Mr. ROSE. Take another look. We haven't had a chance to ask you all the questions that we have, but we would like to supply them for the record.

[The information follows:]

A copy of EPA's Carcinogen Risk Assessment Guidelines and a list of documents on compounds that have been evaluated for carcinogenicity were provided to you in your original request. We will be happy to provide further discussion of such documents if you with.

Mr. ROSE. If you will shepherd that effort to get us that information, we would appreciate it.

Mr. FARLAND. We will be pleased to deal with those questions.

Mr. ROSE. Dr. Bayard, did you have anything to do with the selection of the companies that were contracted with by EPA to do your study, your evaluation?

In other words, you were the Project Manager. Actually, how many contractors out there were working under you?

Mr. BAYARD. Let me try to get to that the best I can.

Mr. ROSE. That is what I want you to do, but quickly. Five, six, 10?

Mr. BAYARD. ICF was a contractor; Battelle was a contractor. Those two, but most of those had subcontractors.

Mr. ROSE. All right. And who made the choice about those two?

Mr. BAYARD. I did not choose——

Mr. ROSE. Beg your pardon? You made the decision?

Mr. BAYARD. To choose ICF? I guess I did, but it was chosen mainly as an umbrella contractor.

Mr. ROSE. Yes.

Mr. BAYARD. I am not the Project Officer on any of those.

Mr. ROSE. You were the Project Manager.

Mr. BAYARD. I am the Project Manager, but not the Project Officer on contracts.

Mr. ROSE. Did they work for you?

Mr. BAYARD. I am a Work Assignment Manager on contracts. I submit the work assignment I want done.

Mr. ROSE. To ICF, is it ICI?

Mr. BAYARD. ICF was one. Battelle was another.

Mr. ROSE. They subcontracted the contract to the Institute for Smoking Policy?

Mr. BAYARD. No. I had nothing to do with that.

Mr. ROSE. That was my question. I didn't ask, did you have anything to do with it. I said the contractor that you picked. ICF, they assigned it?

Mr. BAYARD. The Institute for Smoking Policy had nothing to do with the risk assessment. They had to do with the workplace policy guide. I am here to discuss the risk assessment. I also used contractors from ICF.

If you want, I will be glad to talk about that.

Mr. ROSE. No. You had experience with these people before, had you not?

Mr. BAYARD. ICF?

Mr. ROSE. Yes.

Mr. BAYARD. A very good statistician worked at ICF, we used for the first draft.

Mr. ROSE. We have to go vote. We will be back within a few minutes.

I think Mr. Baesler has a few more questions. We will try to be back within 10 minutes.

[Recess taken.]

Mr. ROSE. The subcommittee will come to order. I will restate for the record that we have a lot of questions that have not been answered, that we would appreciate the Agency responding to us in the usual timely fashion.

Mr. Baesler.

Mr. BAESLER. We have talked about several studies during the day. I would like to talk about one particularly. I notice that the Fontham study—we note in this regard that the revised drafts of the risk assessment dates from fall of 1992, not long after the Fontham study appeared, take the study results fully into the account. You did take the Fontham study results fully into account; is that correct?

Mr. BAYARD. Yes.

Mr. BAESLER. We see among the documents provided a memo stating that even more emphasis needed to be put on the Fontham because it was NCI funded and it was the largest study. Brownson was also NCI funded and even larger than Fontham.

Finally and perhaps most disturbing, we have seen a document in which Kenneth Brown promises Dr. Fontham to hold up the circulation of the revised risk assessment draft until her study ap-

pears in the scientific literature. On October 12, 1991, we see that Kenneth Brown wrote to Dr. Fontham and said of the inclusion, "The time element is of concern to EPA, but I will not violate your request for propriety. Without permission from you I will hold a revised version that includes your study until it appears in print and is thus publicly available."

It is my concern and the committee's concern that you seem to spare no effort to take into account the studies that help your case, but you didn't give the same consideration to studies that didn't help your case. How do you respond to that?

Mr. FARLAND. The report published in December of 1992 listed a number of studies that came out shortly after the Science Advisory Board had looked at our report and had essentially given us a final sign-off. They included Stockwell and Brownson.

As you are probably aware, scientists who are involved in this particular field get preprints of the materials before they are finally published. We had preprints of the Fontham study, preprints of the Brownson study as they were being developed, but there is a reason that one cannot cite certain studies until they have appeared in the published scientific literature. I will let Dr. Bayard speak specifically to the issue of how we dealt with the Fontham study.

We have taken into account the two other studies that were mentioned, particularly Stockwell and Brownson. Both are consistent with our results. They are not at odds with our results, and I think you will see that in our report there is a statement to that effect. So we have not ignored those studies at all.

Mr. BAESLER. Another question on the Fontham study. The risk assessment classifies the Fontham study as tier 1, these being studies that are of greatest utility for investigating a potential association between ETS and lung cancer. You say use of dietary, occupational, and other exposure data in that analysis, along with an additional 2 years of subject accrual, will make the completed study for this, which constitutes an interim report, even more valuable.

From this I understand that you realize that the Fontham study published in 1991 did not attempt to analyze the effect of confounding factors. Since your guidelines for carcinogen risk assessments require you to rule out the possibility that confounding factors might account for an observed increase in risk, I assume that you asked Fontham to undertake analysis of the effects of compounding factors such as diet and previous lung disease, yet I see no communication between EPA and Dr. Fontham in these documents that you supplied to me that discusses this matter. Did you communicate with Dr. Fontham on this matter?

Mr. BAYARD. On the matter of confounding?

Mr. BAESLER. Yes, sir.

Mr. BAYARD. I communicated with Dr. Fontham a lot—not that much—and we talked about confounding. The way the study was designed made it really helpful because there were very few confounders left.

Mr. BAESLER. I will read from the study.

Mr. ROSE. Do you have an answer, sir?

Mr. BAYARD. Yes. We talked to her about workplace, about childhood exposures, about the exposure measurements, about whether or not we should pick population controls or the colon cancer controls. We talked about—there was one more—I am sorry I forget.

Mr. BAESLER. Fontham did appear before the SAB in July 1992 where she stated, the approximate 30 percent risk of lung cancer associated with spousal ETS exposure persisted after adjustments for vegetable consumption which was the most significant food or nutrient factor, family history of lung cancer and employment in high risk occupations or industries.

Whether or not this is correct, these findings have not been published in the peer review literature; have they?

Mr. BAYARD. I think that is correct.

Mr. BAESLER. Moreover, there is no evidence that EPA even thought this analysis to be important, though clearly some of us would think it was.

Also Dr. Wu Williams, a coauthor of the Fontham study, currently has a grant with NCI to undertake the analysis that Fontham said were complete to the SAB; is that correct?

Mr. BAYARD. I don't know.

Mr. BAESLER. Dr. Wu Williams is a coauthor of the Fontham study. He applied to the National Institutes of Health in October 1991 for a grant to analyze the Fontham study data. Dr. Wu Williams' project description includes a proposal to evaluate "the independent effect associated with each of the above factors, indoor air pollution, diet and instances of previous lung disease and its potential confounding effect on the passive smoking lung cancer association."

A summary statement of a special review committee that reviewed the grant proposal of the National Institutes of Health stated that, "given the relatively small risk found for passive smoking, it is critical that ETS possible confounding factors be investigated to determine whether the passive smoke effect is merely the result of confounding or of other variables." This grant was awarded with an initial project period from June 1992 to May 1993.

Were you aware of this?

Mr. BAYARD. No.

Mr. BAESLER. Do you agree with the comments of the NIH Special Review Committee that it is critical that other possible confounding factors be investigated to determine whether the passive smoke effect is merely the result of compounding smoke or other variables? Do you agree with that?

Mr. BAYARD. In the Fontham study or all studies?

Mr. BAESLER. How about the Fontham study and all—include everything. About the Fontham study first.

Mr. BAYARD. My answer is no.

Mr. BAESLER. On both cases, right?

Mr. BAYARD. No. The question was is it critical with respect to our finding whether or not the Fontham study might have had more confounders, and the answer is no because the Fontham study would have been one of 33 studies on epidemiology.

Mr. BAESLER. What steps did you take to insure that the relative risks reported in the Fontham study were not merely the result of

confounding of other variables? Did you take any steps in your study on that?

Mr. BAYARD. We examined every one of the studies where confounders were addressed. We couldn't identify any one confounder that could have possibly been responsible for dose response relationships that we saw or the fact that we saw these increases in all different countries.

For instance, diet changes in every country, and yet we saw the effect of passive smoking in all the countries we looked at, with the exception of China, where the studies were mainly to examine the effects of smoke and other indoor air pollutants.

Mr. BAESLER. It seems to me that there are many doubts surrounding the Fontham study in terms of there being an incomplete report that did analyze for potential confounding factors. I think everybody agrees that there wasn't analyzing for confounding factors. That the study should not have been included in the meta-analysis of the U.S. studies. I gather that a meta-analysis of the U.S. studies, including the two new studies, but excluding Fontham, gives us a statistical nonsignificant summary risk of 1.04. This suggests to me a considerable instability in the data.

How can you claim such confidence in your analysis when slight changes of studies considered have such effects? In other words, if we take out the Fontham study, it seems it changes the whole thing.

Mr. BAYARD. Why would you take out the best study we have available?

Mr. BAESLER. Maybe because they didn't take into account the confounding factors.

Mr. BAYARD. It was a published study in a well-respected journal supported by the National Cancer Institute the same way the Brownson study and Stockwell study were. Why should we take that out?

It seems to me you are just being critical of the studies that were positive.

Mr. BAESLER. Do you think it is relevant that now we have a grant given to study this study and how confounding factors might affect it. The National Cancer Institute has given a grant to study the effect of confounding factors as pointed out by the Fontham study, which you indicate is the best study you had to make your argument and the results of the ETS problem.

Mr. BAYARD. It was the only tier 1 U.S. study, if I am not mistaken. There were several tier 1 studies in other countries.

Mr. BAESLER. Maybe I just don't know enough, but you admit that we didn't do an analysis on what the other confounding effects might have had on Fontham's results?

Mr. BAYARD. If I had had the information on diet, if I had known it existed, I would have done the analysis on confounding.

Mr. BAESLER. You wouldn't do it, but the National Cancer Institute thinks it is relevant enough that they will give a grant to a group of people to do a study that you said wasn't relevant.

Mr. FARLAND. Mr. Baesler, I think it is very important that you understand that we would have follow-up studies on the majority of the epidemiology studies that are published in the literature today. Those studies find information, they develop additional

hypotheses and they suggest additional studies that need to be done. That is the way that the epidemiology work is done.

I think this was a well-designed study that took into account a number of these issues with regard to confounding that many others did not. While there was not a specific analysis of confounding published with that study, I wouldn't argue that the answer was in and that we shouldn't do any additional research.

The authors of the study came into the National Cancer Institute to get an additional study. They may find when they collect more information that the relative risks may go up, they may go down, or are not clear.

Mr. ROSE. One question. Did you do a one-tailed analysis of the Fontham study?

Mr. BAYARD. Yes.

Mr. ROSE. And the issues around confounded hadn't been resolved; is that correct?

Mr. BAYARD. That is correct.

Mr. ROSE. And if you had done a two-tailed study on Fontham, your—what is the——

Mr. BAYARD. Significance level——

Mr. ROSE. Your confidence level would have been 95 percent; right?

Mr. BAYARD. That is correct. It is close enough.

Mr. ROSE. But you did a one-tailed study and essentially your confidence level is 90 with the one-tailed study?

Mr. BAYARD. Yes.

Mr. ROSE. That is all I was trying to get at earlier, Dr. Farland. Why did you have so much trouble answering my question?

Mr. FARLAND. This is a very difficult statistical issue.

Mr. ROSE. I know. Now, if the statistical confidence level of a one-tailed study produces a 1.04, could that number have gone down with a two-tailed study?

Mr. BAYARD. The two-tailed test on the ever versus never, I think, was 0.99, with the 95 percent confidence interval—the lower 90 percent interval was 1.04.

Mr. ROSE. If you had done the two-tailed study, you could have had a confidence level of 95, but your statistical significance could have been below one?

Mr. BAYARD. I know what you mean.

Mr. ROSE. Do you see why we are a little suspicious about this game?

Mr. BAYARD. That is true for the ever versus never.

Mr. ROSE. That is the only American study with any statistical significance and you do a one-tailed study with a 90 percent confidence level. If you had done a two-tailed study, it probably would have been below one. You haven't figured in the confounding factors that we just talked about and yet you issued this report in a hurry between changes in administrations and drive policy in this country from every courthouse, every workplace, every building in America.

I have nothing to argue about the fact that direct smoking can cause serious results in human beings, but when you are in such a hurry to reach a result like this on this kind of weakness, I think we have a right to ask some tough questions.

Dr. Farland, why didn't you go for a separate study, an American Congress funded, whatever, an EPA request for one massive study of this issue in America, do it right, do it long enough, get this issue cleared up once and for all? Why didn't you do that, sir?

Mr. FARLAND. Mr. Chairman, again, these issues have been under discussion in the scientific community for many years. This was not done in a hurry. The evaluation of these 30 studies is a unique data base.

We have very few situations where we have this many studies to work with. I would not argue at all with the need to get additional data on this issue. As a scientist, I agree with you.

Mr. ROSE. How many other countries in the world consider environmental tobacco smoke under their system equivalent to a class A carcinogen? How many other countries in the world?

Mr. FARLAND. I think it is probably most important that the World Health Organization has taken the position that environmental tobacco smoke causes lung cancer.

Mr. ROSE. When did they take that position?

Mr. FARLAND. They took that in 1986, and on the issue of other respiratory disorders in 1992.

Mr. ROSE. How was that conclusion reached?

Mr. FARLAND. The same way that the Surgeon General's conclusion and the National Academy of Sciences conclusion was reached.

Mr. ROSE. Was that on environmental tobacco smoke?

Mr. FARLAND. Yes, it was, with 14 epidemiology studies at that time, not 30, and not nearly of the power of Fontham and Brownson. This is an issue that has been dealt with in the scientific community for a long time. I am certainly willing to answer technical questions about the way that we went through this, but not that we hurried.

Mr. ROSE. I would appreciate it if you would wow me with some data, if you can provide for the record whatever you have on the way in which the World Health Organization reached its conclusion and why you think it was based on sound science. I am sure that is around EPA somewhere since this has been studied so long and so carefully.

Mr. FARLAND. We will provide you with a copy of the report.

[The information follows:]

Copies of the WHO documents are enclosed for your use. All of the WHO documents receive worldwide peer review before publication. The International Agency for Research on Cancer (IARC) document on Tobacco Smoking has been used in numerous countries in establishing policies on smoking.

WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

ON THE

EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Tobacco Smoking

VOLUME 38

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of the Carcinogenic Risk of Chemicals to Humans
which met in Lyon,

12-20 February, 1985

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. In 1980, the programme was expanded to include the evaluation of the carcinogenic risk associated exposures to complex mixtures.

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for chemicals and complex mixtures to which humans are known to be exposed, and on specific occupational exposures, to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields, and to indicate where additional research efforts are needed.

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NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean the probability that exposure to the chemical will lead to cancer in humans.

Inclusion of a chemical in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that a chemical has not yet been evaluated in a monograph does not mean that it is not carcinogenic.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of a chemical to humans is encouraged to make this information available to the Unit of Carcinogen Identification and Evaluation, Division of Environmental Carcinogenesis, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the chemical may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Unit of Carcinogen Identification and Evaluation, so that corrections can be reported in future volumes.

IARC WORKING GROUP ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: TOBACCO SMOKING

Lyon, 12-20 February 1985

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IARC MONOGRAPHS PROGRAMME ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS[1]

PREAMBLE

1. BACKGROUND

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. Following the recommendations of an ad-hoc Working Group, which met in Lyon in 1979 to prepare criteria to select chemicals for *IARC Monographs*(1), the *Monographs* programme was expanded to include consideration of exposures to complex mixtures which may occur, for example, in many occupations or as a result of human habits.

The criteria established in 1971 to evaluate carcinogenic risk to humans were adopted by all the working groups whose deliberations resulted in the first 16 volumes of the *IARC Monographs* series. This preamble reflects subsequent re-evaluation of those criteria by working groups which met in 1977(2), 1978(3), 1982(4) and 1983(5).

2. OBJECTIVE AND SCOPE

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for chemicals, groups of chemicals, industrial processes and other complex mixtures to which humans are known to be exposed, to evaluate the data in terms of human risk with the help of international working groups of experts, and to indicate where additional research efforts are needed. These evaluations are intended to assist national and international authorities in formulating decisions concerning preventive measures. No recommendation is given concerning legislation, since this depends on risk-benefit evaluations, which seem best made by individual governments and/or other international agencies.

[1]This project is supported by PHS Grant No. 1 U01 CA33193-03 awarded by the US National Cancer Institute, Department of Health and Human Services.

The *IARC Monographs* are recognized as an authoritative source of information on the carcinogenicity of environmental and other chemicals. A users' survey, made in 1984, indicated that the monographs are consulted by various agencies in 45 countries. As of March 1986, 38 volumes of the *Monographs* had been published or were in press. Five supplements have been published: two summaries of evaluations of chemicals associated with human cancer, an evaluation of screening assays for carcinogens, and two cross indexes of synonyms and trade names of chemicals evaluated in the series(6).

3. SELECTION OF CHEMICALS AND COMPLEX EXPOSURES FOR MONOGRAPHS

The chemicals (natural and synthetic including those which occur as mixtures and in manufacturing processes) and complex exposures are selected for evaluation on the basis of two main criteria: (a) there is evidence of human exposure, and (b) there is some experimental evidence of carcinogenicity and/or there is some evidence or suspicion of a risk to humans. In certain instances, chemical analogues are also considered. The scientific literature is surveyed for published data relevant to the *Monographs* programme; and the IARC *Survey of Chemicals Being Tested for Carcinogenicity* (7) often indicates those chemicals that may be scheduled for future meetings.

As new data on chemicals for which monographs have already been prepared become available, re-evaluations are made at subsequent meetings, and revised monographs are published.

4. WORKING PROCEDURES

Approximately one year in advance of a meeting of a working group, a list of the substances or complex exposures to be considered is prepared by IARC staff in consultation with other experts. Subsequently, all relevant biological data are collected by IARC; recognized sources of information on chemical carcinogenesis and on-line systems such as CANCERLINE, MEDLINE and TOXLINE are used in conjunction with US Public Health Service Publication No. 149(8). Bibliographical sources for data on mutagenicity and teratogenicity are the Environmental Mutagen Information Center and the Environmental Teratology Information Center, both located at the Oak Ridge National Laboratory, TN, USA.

The major collection of data and the preparation of first drafts for the sections on chemical and physical properties, on production and use, on occurrence, and on analysis are carried out by Tracor Jitco, Inc., and its subcontractor, Technical Resources, Inc., both in Rockville, MD, USA, under a separate contract with the US National Cancer Institute. Most of the data so obtained refer to the USA and Japan; IARC attempts to supplement this information with that from other sources in Europe. Representatives from industrial associations may assist in the preparation of sections describing industrial processes.

Six months before the meeting, articles containing relevant biological data are sent to an expert(s), or are used by IARC staff, to prepare first drafts of the sections on biological effects. The complete drafts are then compiled by IARC staff and sent, prior to the meeting,

to all participants of the Working Group for their comments.

The Working Group meets in Lyon for seven to eight days to discuss and finalize the texts of the monographs and to formulate the evaluations. After the meeting, the master copy of each monograph is verified by consulting the original literature, edited by a professional editor and prepared for reproduction. The aim is to publish monographs within nine months of the Working Group meeting. Each volume of monographs is printed in 4000 copies for distribution to governments, regulatory agencies and interested scientists. The monographs are also available *via* the WHO Distribution and Sales Service.

These procedures are followed for the preparation of most volumes of monographs, which cover chemicals and groups of chemicals; however, they may vary when the subject matter is an industry or life-style factor.

5. DATA FOR EVALUATIONS

With regard to biological data, only reports that have been published or accepted for publication are reviewed by the working groups, although a few exceptions have been made: in certain instances, reports from government agencies that have undergone peer review and are widely available are considered. The monographs do not cite all of the literature on a particular chemical or complex exposure: only those data considered by the Working Group to be relevant to the evaluation of carcinogenic risk to humans are included.

Anyone who is aware of data that have been published or are in press which are relevant to the evaluations of the carcinogenic risk to humans of chemicals or complex exposures for which monographs have appeared is asked to make them available to the Unit of Carcinogen Identification and Evaluation, Division of Environmental Carcinogenesis, International Agency for Research on Cancer, Lyon, France.

6. THE WORKING GROUP

The tasks of the Working Group are five-fold: (a) to ascertain that all data have been collected; (b) to select the data relevant for evaluation; (c) to ensure that the summaries of the data enable the reader to follow the reasoning of the Working Group; (d) to judge the significance of the results of experimental and epidemiological studies; and (e) to make an evaluation of the carcinogenicity of the chemical or complex exposure.

Working Group participants who contributed to the consideration and evaluation of chemicals or complex exposures within a particular volume are listed, with their addresses, at the beginning of each publication. Each member serves as an individual scientist and not as a representative of any organization or government. In addition, observers are often invited from national and international agencies and industrial associations.

(The complete report is held in the committee files.)

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THE INTERACTION OF SMOKING AND WORKPLACE HAZARDS

RISKS TO HEALTH

Office of Occupational Health, and
Tobacco or Health Programme
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THE INTERACTION OF SMOKING AND WORKPLACE HAZARDS

RISKS TO HEALTH

by

K. Rothwell

Consultant, WHO Tobacco or Health Programme, Geneva
and WHO Office for Occupational Health, Geneva

Contents

Preface

The dangerous health consequences of smoking are now well documented, the detrimental effects of many workplace pollutants are also recognized. Clearly one hazard will not negate the other and injury could be sustained from both causes. It is also obvious that any tissue that has suffered insult from a harmful agent might be more seriously damaged if it were also subjected to attack from another one.

It has been found in several situations that smoking and industrial hazards may not only each add a contribution to an ultimate ill health effect but that each can modify the effect of the other to result in a more serious disease condition.

This document summarizes some observed interactions between smoking and some occupational hazards. It does not exhaustively explore the effect of smoking on occupational diseases, because in many industrial situations the effect of a combination of the two hazards has never been surveyed, and it gives a few examples only for the small number of industries that have been extensively studied.

THE RISK TO HEALTH FROM SMOKING AT WORK

Introduction

There are no longer doubts that tobacco use, particularly cigarette smoking, is the principal cause of several debilitating and often terminal diseases. It has also long been recognized that the workplace is a source of hazards that can cause disease and early death in many occupations. During the past two decades it has become clear that when workers smoke at their place of work, they are not merely exposed to two mutually isolated types of hazard: one attributable to the occupation and the other to tobacco smoke, but are subject to detrimental health effects arising either from a combination or from an interaction of the two.

Tobacco is used throughout the world; in countries with low income economies and in the most affluent industrialized nations. It is used by men and women, by children and adults, and millions of others are involuntarily subjected to environmental tobacco smoke. There are numerous explanations for the tobacco habit but the main reason for its ubiquity is the addictive drug nicotine present in all forms of tobacco leaf and delivered in varying amounts to the user by all the methods of usage that people worldwide have, over the ages, devised.

In many lesser developed countries, and particularly in the rural areas of these countries, traditional methods of tobacco use are widely practised but are being supplanted by cigarette smoking; a habit which by and large has replaced all other forms of use in the industrialized countries. Traditional ways of using tobacco have been legion but are all based on either smoking tobacco in some form of pipe or hand rolled tube of tobacco, or on chewing a mixture of tobacco with a variety of flavouring materials. The cigarette appeared and began to replace such methods of use in Europe, possibly as an imitation of papyrosi, after the Crimean War, and records dating back as far as the 1880's detail cigarette consumption in France and the United Kingdom from then to the present day. The reasons for the popularity of cigarette smoking emerging in Europe and the USA were probably twofold; on the one hand availability following the invention of a machine for large scale cigarette manufacture, and on the other, the greater ease and convenience that cigarettes brought to tobacco use. By the end of the second world war, cigarette smoking had become completely established as a socially acceptable habit for both men and women in the developed countries where, for a period during the 1950's, there may have been more smokers than non smokers. Today, in most developed countries, cigarettes account for at least 80% of the overall tobacco consumption and in most developing countries cigarette smoking is increasing rapidly and, in all but the poorest and most remote areas, is replacing other forms of tobacco use.

During the past 40 years, smoking has been recognized as being a serious health hazard and the main cause of death from many common diseases in most developed countries. In these countries, where the effects of smoking on health are generally appreciated and the economic costs and losses realized, legislation is being enacted, control is being taken through taxation, and action is being taken to educate the public not only on the dangers of smoking but also on the benefits to be gained from stopping. In only a small number of developing countries have the hazards and economic disadvantages that are associated with widespread tobacco use by the population been fully accepted even at government level, and there are not many of these countries that have as yet taken any decisive action to curtail the behaviour.

All working situations involve an element of danger: frequently it is associated with accidents, but harmful health effects often arise from the work itself, or in the environment of the working activities. Thus there are airborne mineral dusts in mining and biological dusts in farming and industries using biologically produced raw materials; fume is produced during welding; smokes, mists, vapours and gases present hazards in many industrial situations; excessive heat, ultra violet light and high levels of noise are frequently detrimental to the well being of workers; ionizing radiations in mining and modern technology are now recognized as workplace hazards and in many occupations workers are subjected to harmful mechanical vibration. These occupational conditions all take their toll on health and well-being but it is now also realized that their effects are far greater when they are combined with the added effects from tobacco smoking.

Tobacco growing involves the use of chemical agents which can harm the health of workers; harvesting can cause sickness due to skin absorption of nicotine; and processing exposes workers to health hazards from airborne dust and fungal spores. However, the greatest impact of tobacco on the health of the workforce as a whole is in the effects of smoking on other diseases related to the workplace. Smoking, particularly cigarette smoking, is detrimental to health in a wide variety of occupations not only because of the diseases it causes *per se* but because it adversely affects disease conditions in which other agent(s) may be aetiologically implicated. It has become clear that work hazards and the hazards associated with smoking at work cannot be separated, nor considered in isolation in the workplace. Apart from the now well known danger to non smokers of the smoking by coworkers being allowed to contaminate the shared atmosphere, there are other situations where smoking increases the severity of a disease to a level far in excess of what could be expected from smoking alone, from the occupational hazard alone, or even from the two effects added together.

In many industrialized countries, the hazards of the workplace have been recognized, regulations have been formulated and legislation has been enacted to protect workers and

provide for their education on the dangers arising from the nature of the occupations in which they are engaged; although in some countries, implementation of the rules and law is not always strictly imposed and workers sometimes neglect the training they have been given. In many newly industrialized countries where development is progressing swiftly, the health problems associated with the work have not yet been addressed and many workers are completely ignorant of the dangers to their health by which they are surrounded.

In most countries and in many working situations, the combined effects on health of smoking and occupational hazards have as yet been seldom fully recognized, or accepted by governments, employers, unions, or workers and the dangers of smoking at work have not been given serious attention except where there might be risks of large scale accidents from fire or explosion.

It is hoped that the following brief survey of the interaction of smoking with the hazards of the workplace will serve to illuminate some aspects of the situation and stimulate further research into problems which can affect not only the health of individuals but also the economic success of many industries and ultimately national economies.

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7. Summary and conclusions

Many harmful effects of smoking are now well documented and have been overwhelmingly substantiated. There have been a considerable number of investigations of the interaction of smoking with and the health hazards found in various occupations and this short survey has reviewed some of the risks that have been associated with smoking in the workplace. Several subjects have not been dealt with in any detail, such as: allergic reactions and sensitization; certain cardiovascular diseases; effects involving cell division; the effects of smoking on concentration, performance and efficiency, on sight, on the autonomic nervous system, on systems of detoxification and on reproduction. Although there is information concerning occupational hazards in these areas, and the effect of smoking is known in some, further research on the interaction of the hazards is needed.

There is now considerable information on the ways in which smoking and many industrial hazards interact to cause increases in severity or more rapid onset of

diseases, and yet an impression gained from all the studies is that the harm occasioned by smoking outweighs that for all other agents, and in some cases it is difficult to avoid the conclusion that if damage to tissues from smoking had not occurred, the effects of workplace hazards would have been far less severe.

It is known that:

- Involuntary smokers, teenage smokers, and children in households where there are smokers, suffer from pulmonary dysfunction which can be equated with small airways disease.

- Smoking has a detrimental effect on mucus secretion, mucus quality and lung clearance.

- Smoking surveys in many countries have shown a high prevalence of addicted smokers among teenagers, and most habitual smokers start the habit as teenagers.

The inevitable conclusion from these facts is that an enormous number of young people suffer from small airways inflammation and impairment of their lung clearance mechanism solely from tobacco smoke and this occurs before they ever encounter any occupational hazards. Questions arise, therefore, on the role of smoking related disabilities as precursors of many other diseases, particularly the occupational diseases. It seems reasonable to suppose that any hazardous material encountering tissue that is already suffering some degree of inflammation due to smoking will have a more profound effect than if it were to impinge upon normal healthy tissue. Furthermore if harmful inhaled materials cannot be efficiently cleared, because smoking has damaged the clearance mechanism, within a short time of being deposited, their longer term residence in the respiratory system will occasion greater harm than if they had been rapidly removed.

In all countries where surveys have been carried out, the highest prevalence of smoking is among the so called "blue collar workers" and from many of the studies cited in this document, it is seen that there is invariably a very high prevalence of smoking among workers who are involved in jobs where dusts are generated. Thus, most workers are susceptible to the effects of dust when they first join the work force and reinforce their susceptibility throughout their working lives.

The inevitable conclusions from this review are:

1. Tobacco smoke can modify the risk associated with many hazardous materials encountered in the workplace and in some cases the interaction causes an extraordinary increase in the severity of the disease, often advancing its onset and accelerating its rate of development.

2. Chemical substances associated with health risks are often present in both cigarette smoke and in the working environment and thus each source can add to the burden imposed by the other to increase the severity of a disease.

3. Harmful materials in the workplace can contaminate smoking materials and be transferred from there to the user, in some cases causing severely debilitating and possibly life threatening diseases.

4. Innocuous materials in the workplace can be transformed by the smoking process into extremely harmful compounds.

5. The effects of smoking on the vascular, particularly the peripheral vascular, system can considerably enhance the diseases which affect the extremities and impair the use of the hands and also affect hearing acuity.

6. Passive smoking is invariably a workplace hazard whether the smoke is the only atmospheric contaminant or occurs in combination with other workplace pollutants.

7. All diseases suffered by a work force, whether caused by smoking or caused by industrial hazards, or enhanced by interaction of the two, result in absenteeism, often lead to early retirement due to disability, reduce productivity and increase employers costs. Thus the worker is put under financial stress and the employer, suffering work disruption and the loss of skilled labour, encounters economic loss. Ultimately the economic losses are reflected in national economies which are at further disadvantage because of the economic costs associated with these diseases that arise from increased medical service costs and increases in the costs of social benefits.

8. A complete ban on smoking in all places of work would be advantageous to all concerned.

(The complete report is held in the committee files.)

Mr. BAESLER. I would like to walk back through some of the testimony and see if I am correct. Dr. Bayard started with a feeling there was a problem. I think that has been in the record.

Mr. BAYARD. I corrected myself, sir.

Mr. ROSE. He asks unanimous consent to revise and extend.

Mr. BAESLER. You start with that feeling. Then as testimony further came out that we had criticisms from different groups like the Cincinnati group, we said they were criticisms but we sort of disregarded them. Whether you said you disregarded them or not, you disregarded them. We let them decide because they didn't agree with the conclusion.

Then we have the studies coming in, we picked the No. 1 study, the Fontham study, the best one I think you said, tier 1, a good study. In it, it suggests that there might have been some problems with the confounding factors of vegetables or whatever, and we said well, we didn't go get that tested because we didn't think that was important even though somebody, some organization as prominent as the Cancer Institute evidently thinks it is important, because they gave money to study it. So that bothers me.

Maybe I am just cynical, but all the way through this, it seems we have always gone back that we had this feeling and everything we have done since then that doesn't substantiate the feeling is sort of disregard this second tier information. Only a court case will tell whether that is right or wrong.

From a pure nonscience perspective from what I have heard today, there were two other studies available prior to the 1992 that weren't considered as much. Maybe I am talking about the Brownson or something.

Mr. FARLAND. Brownson and Stockwell, perhaps.

Mr. BAESLER. You didn't give as much weight. You said they did support what you had.

Mr. FARLAND. They were not published until after the report.

Mr. BAESLER. This lady's wasn't published and you took hers into consideration, Fontham.

Mr. BAYARD. We didn't know the Stockwell study existed at that time.

Mr. BAESLER. Fontham was not only not published. You were going to wait until she published it. Here is a letter—your interim study report has created a lot of interest at EPA and they would like me to include it in my report and I fully support this idea, and we will wait. So whether it has been published has nothing to do with it.

Mr. FARLAND. If I could just give you a quote from our report that was published. It is after page 8–16, called ADD–1, it was an addendum. It says pertinent new studies, "Several pertinent studies on the respiratory health effects of passive smoking have appeared since the cut-off date for inclusion in this report. The studies are cited here for the benefit of anyone who may wish to follow-up on these topics. The studies are briefly described below and the author's conclusions are presented. We do not formally review these studies in the report and the citations do not represent a full literature search. These new studies are generally consistent with this report's conclusions that environmental tobacco smoke expo-

sure increases the risk of lung cancer in nonsmokers and affects the respiratory health of infants."

The quote on the Stockwell study, Stockwell concluded that long-term exposure to ETS increases the risk of lung cancer in women who have never smoked. That is directly from the Stockwell study. And from the Brownson study, ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking. That was included in the report that we published.

Mr. BAESLER. I think you concluded that it was part of the study.

If I understood what you said earlier, the area, you tried it out to make sure it worked was in the home, the spouse.

Mr. FARLAND. Those are the most powerful studies that were available to us.

Mr. BAESLER. They were the thrust from which you could reach a conclusion.

Mr. FARLAND. The scientific community agrees that those are the cohorts that can be examined for this particular effect.

Mr. BAESLER. A question was asked about workplace and I thought somebody said we are talking about in-house spousal things here.

Mr. FARLAND. That is the basis for those 30 studies. There are workplace studies. There are other studies out there.

Mr. BAESLER. I am not worried about those. I am worried about your conclusions that were based on in-house, the spousal situations in the home?

Mr. FARLAND. Never smoking women.

Mr. BAESLER. Tell me if I am right. The last question—your conclusions that ETS can cause cancer for those who are in a room with it are primarily based on spousal situations in the home?

Mr. FARLAND. Mr. Baesler, as I showed on the chart, there were some five or six legs of this analysis and the 30 epidemiology studies were only one of those legs.

Mr. BAESLER. But it was not the most important?

Mr. FARLAND. It was one of the important areas.

Mr. BAESLER. I am through. I still don't know much more than I started out knowing. My conclusion is that—still I go back to it seems like a cavalier approach to a very serious issue that has caused tremendous damage to a lot of our people.

Mr. ROSE. Dr. Farland, would you supply for the record what countries on this planet have classified environmental tobacco smoke under their grading system or prioritizing system, the equivalent of what you call a class A carcinogen?

Mr. FARLAND. Mr. Chairman, I will try to get that information for you.

[The information follows:]

To the best of our knowledge, the only country that has done an independent evaluation of the health effects of environmental tobacco smoke is Australia. The National Health and Medical Research Council of Australia completed an assessment of tobacco smoke several years ago, and, we understand, is currently doing another evaluation. We do not know if a carcinogenic classification was used by the Australians. We are attempting to find that out.

Mr. ROSE. I appreciate what you said about the World Health Organization, but that still doesn't answer my original question,

and you still haven't. You basically feel that there was not a need to do new research?

Mr. FARLAND. No. I stated that I would agree that we need to have additional research.

Mr. ROSE. But you felt that this new look at all of these 30-some studies was sufficient to reach this conclusion?

Mr. FARLAND. We did. That is right.

In 1986, others made those same conclusions on 14 studies as well as all the other information. In 1992–1993, we made that conclusion on some 30 studies.

Mr. ROSE. Can you supply for the record what other studies you think should be done if EPA had sufficient funding to pay for them to verify the conclusions you have reached in this study?

Mr. FARLAND. I think one of the benefits of doing risk assessment is it points out the critical needs. We will be glad to supply suggestions of some critical needs in this particular area.

Mr. ROSE. Thank you all very much. The panel is excused.

Mr. FARLAND. Thank you, Mr. Chairman.

[The information follows:]

We can suggest no studies that would be needed to verify the conclusions which we have drawn. Several studies on environmental tobacco smoke are ongoing, and we will continue to follow such studies.

Mr. ROSE. Our next panel is Dr. Alvan Feinstein, sterling professor of medicine and epidemiology at the Yale School of Medicine, New Haven, Connecticut; and Dr. Michael Guerin, analytical chemistry division, Oak Ridge National Laboratories, Oak Ridge, Tennessee.

I apologize for keeping you here so long, but as you can tell, this has been an interesting discussion.

Dr. Feinstein, do you want to begin by using the slide projector?

Dr. FEINSTEIN. I can begin shortly.

Mr. ROSE. All right. I would tell our visitors from the media we are going to have to cut all the lights off now, the TV lights, because we will come back in just a minute with questions, and you can certainly have your lights on then.

STATEMENT OF ALVAN R. FEINSTEIN, M.D., STERLING PROFESSOR, MEDICINE AND EPIDEMIOLOGY, YALE SCHOOL OF MEDICINE

Dr. FEINSTEIN. Mr. Chairman, I have learned a new thing today in the first congressional hearing I have ever attended. I always thought in the past that I could tell where I was from the visual aids.

At a scientific meeting, if they were using flip-over transparencies, the speakers were usually statisticians. If they were handing out thick packages of data, it was usually epidemiologists. If they were using slides, they were usually physicians. If they had big charts and large public relation announcements, I discovered today that it is a congressional hearing.

I shall use the slides that are the medium with which I am most familiar, and I thank you for letting me use them. Before showing slides on some of the problems in making scientific and statistical conclusions, I have another comment.

Some of my statistician friends say that statisticians are like lawyers. They can make a case for the plaintiff or they can make a case for the defense. If you are a good lawyer, you can figure out which way to support either side. Because statistics can be used to support one side or the other, the development and maintenance of scientific standards rather than simply statistical matters, are particularly important.

I would also say that I am absolutely delighted not to be asked to try to explain issues in statistical inference. I feel enormously sympathetic to the folks from the EPA who were earlier at this session given the daunting task of trying to explain issues in statistical inference. If you, as Congresspersons, had difficulty understanding them, you were not alone. Many people in the world of science and most people in the world of medicine are equally confused by the statistical issues of what is significance, what is "confidence" when you talk about "confidence," what are the uriniferous effects of P values, and so on? So don't be upset if you have had difficulty following the explanations. Your difficulty is not unique.

What I wanted to talk about are some of the issues in judging causation. Back in 1964, in the Surgeon General's famous report, they used what is often called either the Surgeon General's or the Bradford Hill criteria. This was the report in which active cigarette smoking was associated with lung cancer and with coronary disease. The authors made two very important points for the criteria that they used.

One point was an entity called the consistency of the association. It meant that in the various different reports, there ought to be very few or no contradictions. In fact, in the association betweem active smoking and lung cancer, 27 out of 29 retrospective studies, and 7 out of 7 prospective studies, all went in the same direction.

The second criterion used by the Surgeon General's committee dealt with the strength of the association. They asked for a so-called dose-response relationship and they wanted high relative risk ratios. For lung cancer, it turned out the risk ratios were 9 to 10 in average smokers and more than 20 in heavy smokers. The demand for high-risk ratios has made various distinguished scientists and epidemiologists—such as Ernst Wynder, perhaps the first person to document the original association between active smoking and lung cancer—demand that for a risk ratio to be meaningful, it must be more than trivially elevated.

It has to be well above two, and preferably above three. The reason for asking risk ratios to be perhaps at least three and certainly much higher than two is that there are too many ways in which different kinds of biases can get into epidemiologic data. You can get a risk ratio of two in some instances if just one person has been misdiagnosed. Therefore, to be confident of things, the usual demand for high-risk ratios is that they be preferably above three and certainly well above two.

Most of my comments here deal with issues of scientific evaluation for the 21st century. I know that the tobacco industry and EPA are involved in mortal combat in this matter, but I am trying to address a more general issue. What kinds of scientific standards are we going to set as all kinds of risks become suspected every day

for our new forms of technology? What scientific strategies do we use for evaluating the risks?

If we consider the two Surgeon General criteria agreed upon back in 1964, both of those criteria were abandoned in the EPA report. They neglected the criterion for consistency and they neglected the criterion for strength. The EPA report pooled a set of inconsistent and low relative-risk studies. I am talking about data from table 5–4 of the EPA report where they established the so-called relationship between passive smoking and lung cancer.

The studies we have been hearing about this morning had six in which the relative risk was below one. They went in the opposite direction. There were 14 where the relative risk was between 1 and 1.49, of which three were statistically significant at a 90 percent confidence level. There were eight in the relative risk range from 1.5 to 1.99, with only three of them being significant even at the lower confidence level. There were seven that went from 2 to .2.5.

This is certainly a melange of inconsistent results. You have six going definitely the other way. You have 14 that barely exceed a ratio of one and you have another 15 that go above 1.5, but none of the risk ratios goes above 2.5. None gets to three or above. Yet those inconsistent studies, contrary to the agreed-upon consistency demanded in the Surgeon General's report, were pooled and put together as though they all went in the same direction.

Now we come to the issue of statistical significance. I am sorry to harass you further with this topic, but I might be able to possibly clarify some of it. There are certain traditional criteria that are called an alpha level of .05 set up for two-tailed P values. The reciprocal of that is a one minus alpha level of .95 that was set up for two-tailed confidence intervals. This is where we get the idea of a 95 percent confidence interval.

The idea of alpha being .05 was an arbitrary custom established by Sir Ronald Fisher who, according to your viewpoint, is either the deity or at least one of the major popes of biostatistics. Like many other standards, the .05 and .95 levels are arbitrary.

I suspect if Fisher said .04 and had gotten there first with his recommendations, they would have been carved in stone. But .05 got there and is being almost universally accepted and demanded by editors, and by agencies such as FDA and NIH.

It may or may not be a good criterion. It may or may not need flexibile adaptations, but if you are going to work in a world that sets certain standards, .05 is the one that has been generally used.

There is an argument that it could be changed to a one-tail alpha of 0.1. This is how you get, in essence, from 95 to 90 percent for the confidence intervals if appropriate hypotheses and plans are clearly stated in advance of the analysis.

Almost every statistician I know who is ready to descend to accept an alpha of 0.1 demands that the investigators have stated in writing, before any analyses, that this is the way they wanted to go. I am not aware of any such advance statement by the EPA, and it seems clear that they were pretty flexible about their boundary because, as Dr. Bayard stated this morning, they did use 95 percent intervals for other analyses. So it seems reasonable when they used an alpha of 0.1 for the 90 percent confidence intervals, the de-

cision must have occurred because the results didn't get statistical significance at .05.

The tactic is reminiscent of the old principle that says "When you got it, flaunt it; and when you don't got it, try to buff it." It seems reasonable that if the EPA analysts had obtained "significance" with 95 percent confidence, that is how they would have put it. I know of no investigators anywhere who drop to 90 percent when they can hit bingo at 95 percent.

Now one of the most interesting aspects to me, in the EPA data of table 5.8 in their meta-analysis, was that they pooled the results for six countries: Greece, Hong Kong, Japan, United States, Western Europe, and China.

When you look at the pooled relative risks in those countries, none of them range above two. The value is .95 in China. When you look at the lower bound of the 90 percent confidence interval, which is the boundary you want to look at, it has to exceed one for you to claim the result is statistically significant.

If you look at those boundaries in Europe and China you might say that the risk is going the other way. In the United States, with a pooled relative risk of 1.19, the lower bound got to 1.04. This is about as close as you can shave above the level of one without actually getting to it. You can feel sure that with a 95 percent confidence interval, the lower bound, would go below one; and the result would not be statistically significant.

In the other three countries, it is hard to tell how low the lower limits would have gone had 95 percent intervals been used. Alas, the Agency did not report what they got with 95 percent intervals, so we don't know whether any of these ratio's would have been statistically significant if the 95 percent level had been used for the other data.

Now, we have heard a little today about meta-analysis. I won't go into the controversy about it, but I can certainly say it is a controversial method. It is not anything about which there is accepted consensus, and the feelings about it range from those who say it is basically statistical alchemy or witchcraft, to those who revere it as a great contribution to modern science, but it is certainly controversial.

In general, there is consensus that you can combine the results for meta-analysis if they come from randomized trials. Randomized trials are the kind of things that drug companies have to do when they test medication and want to claim that different medications are beneficial. Randomized trials are especially designed to avoid the various biases, confounding factors, and intellectual miscreants that can occur in epidemiologic studies.

Meta-analyses that are likely to receive general acceptance are the ones where the original studies come from randomized trials. This is also an arbitrary criterion, but it does receive widespread acceptance in medical literature. If the results do not come from randomized trials—and that means they are coming from epidemiologic studies—the argument is that the investigators must establish special criteria. One of them is to avoid publication bias. It arises from studies that were out there, but that didn't get published or didn't get reported. Another demand is to focus on studies that used their own internal construction mechanisms to avoid de-

tection bias. In other words, was lung cancer identified the same way in both groups? Were outcomes such as asthma or heart disease also identified equally in both groups being compared. Did the individual investigators try to avoid ascertainment bias, which can arise when you interview people to find out who was exposed or not exposed to passive smoke? Did the interviewers know the hypothesis that the investigator was trying to prove? Did the interviewed persons know whether they were cases or controls? What efforts were made to avoid biased interviewing and ascertainment when the interviewing was done?

In the EPA meta-analysis, alas, none of the studies whatsoever were done as randomized trials. Furthermore, no analytic strategies were used by the EPA group to identify or reduce prominent sources of bias, because the EPA group wasn't really doing research here. The EPA was acting as an analyst and processor of the available studies that had been done by other groups. The EPA was, in essence, writing editorials.

Any kind of meta-analysis is a type of editorial in which you depend on the news that has been provided by other investigators. The "news" contained in all the studies came from work done essentially as classical epidemiologic studies, in which almost no provision is made to deal with bias in the interviewing and to deal with bias in issues of detecting the so-called outcome event.

A good many other scientific problems can be mentioned here. You have heard comments, and some of the Congresspersons have themselves made comments, about the studies that were included or excluded in the meta-analysis. I have not tried to go through all of the details with a fine-tooth comb, but it seems clear that certain studies were included or excluded, and that selective choices were made. No matter how they were chosen, however, there doesn't seem to have been an absolutely full deck of all the pertinent things that were available.

The problem of the accuracy of identifying exposure is one of the fundamental scientific lesions in all epidemiologic studies, when the so-called case control technique—which was used in most of the EPA studies—is used to interrogate "backward" in asking people about their exposure. When the investigators and interviewers know what they are looking for, extreme precautions must be taken to avoid bias in ascertaining exposure.

When my colleagues and I do case control studies, we set up a bunch of decoy hypotheses, and we try to "blind" our interviewers from knowing who is a case or control. We even try to "blind" the patients also. We take many kinds of precautions to avoid ascertainment bias, but as far as I know, no such precautions were used in any of the basic studies that the EPA collected.

In one study that absolutely fascinates me, the relative risk for coronary disease was higher for passive than for active smoking. If you believe the results of that study, I await some kind of advertisement from the tobacco industry saying that if you are exposed to passive smoke, you can avoid coronary disease by becoming an active smoker.

There were various other inconsistencies that I won't take time to go through in the passive smoking results for the various cell types of lung cancer. Lung cancer has different kinds of cell types

under the microscope, called epidermoid, adeno, small cell, large cell, and so on. It is like dividing hair color brunettes, blonds, strawberry blonds, and black hair, with the small-cell "strawberry blonds" being the most dangerous. At any event, if passive smoking is actually causing lung cancer, the results ought to be consistent among these different cell types. Yet there are many inconsistencies in the passive-smoking data on that subject.

There are just a couple of other things that I wanted to comment on. The first is the role of the Science Advisory Board. I wasn't quite sure of just what their role was, but I happened to be at a meeting last week attended by Jan Stolwijk, a colleague of mine at Yale, who was one of the members of the Science Advisory Board. Stolwijk made the comment that the Science Advisory Board had urged the EPA not to make its claims about 3,000 extra lung cancers. Nevertheless, the EPA went ahead and made that claim.

I asked Stolwijk "How many other urgings by your committee were disregarded?" He said "Well, I don't want to go into that." So I am not sure about the exact role and interplay of the SAB and EPA groups, but I have great respect for my colleagues. I would not necessarily want to hold the EPA to blame, or to hold the Science Advisory Board responsible for having approved everything that the EPA did.

Finally, in reference to some of the studies on asthma and other symptoms in children, I am always mindful of work done by Dr. Walter Spitzer, a professor of epidemiology and health at McGill University. The research was done in Alberta some years ago on the topic of symptoms that are unaccompanied by objective evidence.

For many years in the Province of Alberta, Canada, there had been complaints about sour gas whose fumes from a nearby mine were coming into a particular community. For a great many years there had been debates and claims that exposure to the sour gas was causing birth defects, cancers, and other problems in residents of that community.

Finally after about 10 years of claims, counterclaims, and battles—not unlike what we have been observing in the ETS issue—the Province of Alberta funded a large-scale study led by Walter Spitzer. The work was eventually published under the title of "Subjective Fears and Objective Data." Spitzer's group conducted what I believe is one of the best epidemiologic studies ever done: superb choices of control groups, blind interviewing and examining—and all the appropriate scientific precautions that could be taken.

The results of those scientific precautions showed that there was no excess of birth defects, no excess of cancer, and no excess of any disease that could be objectively identified. There was an excess of subjective symptoms however. They were present in people in the community where the sour gas had been highly heralded as an evil, but the excess was not found in a control community that received the same alleged exposure, but it had not been publicized as an evil phenomenon.

So with respect to some of these symptomatic studies, I won't deny what was found, but I would also like to see the results of studies where there was careful and unbiased interviewing, where there was a careful and unbiased ascertainment process, rath-

er than merely having a questionnaire filled out and sent through the computer.

My last comment really repeats something that I believe several of the Congressmen have already said. The decisions made for public policy ought to depend on the goals of public policy. If we as a nation want to get rid of cigarette smoking as a matter of public policy, let's make that decision as a matter of public policy; but the scientific evidence used in public policy ought to depend upon the standards of science. Neither science nor public policy is well served if the integrity of science is sacrificed to meet the goals of public policy.

That is the end of what I have to say, sir.

Mr. BAESLER [assuming chair]. We will go to Dr. Guerin now and then we will get to questions.

STATEMENT OF MICHAEL R. GUERIN, ANALYTICAL CHEMISTRY DIVISION, OAK RIDGE NATIONAL LABORATORY

Mr. GUERIN. I bring a chemistry background to the table, and I think that the most important components of the study are the epidemiology and risk assessment methodology which are being discussed and others are more qualified to address than I.

As I mention in my written statement in terms of an overall assessment of the study, I was impressed with the scope of the study and documentation on the issues that were considered, but generally felt the conclusions were presented with a much higher degree of certainty than was justified and this is largely because of the many uncertainties acknowledged in the report itself and the many assumptions made in reaching their conclusions.

The most important probably are the relationship between active and passive smoking and the relationship of spousal exposure to population exposure. From my view, given the very small effect that has been detected assumptions of uncertainties such as this should be worrisome.

The EPA though has taken on a very complicated and difficult task in this assessment. For example, even the very seemingly simple question, what is ETS, is difficult to answer and there was discussion about that earlier today.

ETS is obviously the material in an obviously smoke-filled room, but is it also the residual material that is present in that room hours after smoking. ETS migrates throughout the indoor environment and as it does, it changes in concentration and composition.

So when is ETS no longer ETS? A related question is whether there is a difference in health risk associated with a brief exposure to a high concentration of ETS versus a long chronic exposure to a low concentration of ETS.

It should be noted that most common measures of exposure generally don't detect those kinds of temporal effects. My personal bias is that ETS at some level of exposure is a human carcinogen, but I do not believe that the EPA study proves that and I can't prove that and therefore particularly in view of the EPA study assumptions, it is not possible at this stage to classify ETS as a known human carcinogen.

If the epidemiological findings on the other hand of spousal exposure are deemed to be correct and significant, then ETS can be

classified as a known human carcinogen, but ETS will have to be defined as that material due to cigarette smoking which exists in a residential environment as encountered by a spouse.

In my opinion, the importance of this study combined with the questions that are raised indicates that a formal independent review of the data or of the report may be warranted. That review could possibly include consideration of data or information that is now available that wasn't available at the time of the report.

Another serious need is for a study which experimentally determines the exposure profile of the general population before it is possible to calculate population risks. That particular study should, I think, include measures of ETS and measures of cotinine in urine.

Thank you, Mr. Chairman. I am open to questions.

[The prepared statement of Mr. Guerin appears at the conclusion of the hearing.]

Mr. BAESLER. First, Dr. Feinstein, I gather that—I think it is important for the record that you have just received a prestigeous award for your work in the field of epidemiology. What was it and what are your research interests?

Dr. FEINSTEIN. My research interests are in a field that I call clinical epidemiology. I recently was one of five scientists honored by the Gairdner Foundation in Canada, giving its annual international awards for scientific achievement. The other four were honored for things they had done in various aspects of molecular biology.

I think the citation on my award says it is for leadership in developing clinical epidemiology as a scientific discipline.

Mr. BAESLER. Thank you.

I will turn it back over to the Chair.

Mr. ROSE [resuming chair]. What are your general opinions on the quality of the science in EPA's risk assessment of environmental tobacco smoke? If this document were submitted to you as a term paper or a thesis at Yale, how would you grade it?

Dr. FEINSTEIN. Well, let me be clear now. I made the comment, sir, I think when you were out of the room, that the EPA group did not really do any research. Meta-analyses are not, in my general opinion, doing research. Research was done by the investigators who went and got the original data that were in the original studies that were pooled for the EPA's meta-analysis.

In my opinion, those original studies were not well done. If a student were submitting this work to me, I would say "Can't you do any better than this?"

Mr. ROSE. If you are—well, you are one of the editors of the Scientific Journal entitled "Clinical Epidemiology". What would your journal do with a paper that in its first draft reviewed epidemiologic studies at 5 percent confidence, was sent back to the office for revision and when it was returned reviewed the same studies using a 90 percent confidence interval?

Dr. FEINSTEIN. We would think that the authors were extremely adept academic salesmen whose strategies we had previously encountered. It is not an unique thing to try to put your best foot forward and to try to get your confidence levels to be the best you can get. For example, in expressing what was found, investigators will

usually make things as dramatic as possible. Thus, in a very respectable clinical trial, a mortality rate of 4 percent may be lowered to 2 percent. The result then gets reported by the investigators, by the New England Journal and above the fold in the front page of the New York Times as a 50 percent reduction in mortality rates, which is true.

It is a much more exciting statement, however, than saying the death rate was lowered from 4 percent to 2 percent, which is equally true.

If we received the manuscript you described, we would, I suppose, ask the researchers to try to justify exactly why they did what they did. We would probably say "You really can't make this change after you have looked at the data. You should have proposed it way up front in your original protocol."

To say that everybody may suspect a one-tail direction is probably true, but even so, it should be stated right into the original protocol.

Mr. ROSE. We have heard from former Administrator Reilly at EPA that the change from 95 percent to 90 percent confidence intervals was "At the request of the scientific community." Yet we have also seen that not one of the documents submitted by the Agency to this subcommittee gives any evidence of a request for such a change or indeed discusses it in any way before the fact.

Do you think the change was warranted? What impact does the change have on the risk assessment, and have you any ideas as to why EPA made this change? You may have partially answered some of that.

Dr. FEINSTEIN. First, sir, I don't understand the term "scientific community."

Mr. ROSE. I don't either.

Dr. FEINSTEIN. What is it and where is it located? Is it in Woodstock, New York? Is it just outside of Fayetteville? Where is this scientific community?

Mr. ROSE. It is not there, I can tell you that, but go ahead.

Dr. FEINSTEIN. I keep hearing about Congressmen advocating things. Why don't you get one set up in Fayetteville, sir?

Mr. ROSE. I will do my best.

Dr. FEINSTEIN. So I don't know exactly what is meant by the scientific community. Usually when most people I know talk about the scientific community, what they are saying is my friends, or the folks I went to dinner with, or the ones who attended the last meeting that I went to and whom I chatted with.

In general, I think that this is what that term means. Some folks will restrict the idea of scientific community to those people who I know will agree with me.

I would say that the change of confidence interval from 95 to 90 percent will have a great deal of impact in the future. I am not talking about the particular issue of ETS and cancer or any other ailments that ETS is allegedly causing. I am just talking about the challenges to be met as we get into the future when we start dealing with new kinds of agriculture, where there has been some sort of genetic manipulation, where there are new forms of biodegradability, where there are new forms of biopesticides rather than chemical pesticides. When we then have to evaluate the con-

sequences and risks of these advances, the confidence intervals can be manipulated by almost anybody who wants to get up and wave any banner they want.

For example, I give a group of research fellows, with whom I lead an annual seminar, a particular challenge each year. The challenge is to look through the Statistical Abstract of the United States—a publication that I believe is published by the Congress—and pluck out data to support the most outrageously, silly contention you can come up with. Also find some other plausible new contention that won't seem outrageously silly but that can be put together just by massaging those data.

We give a little prize each year to the person that comes up with the best contrivance. The one this year was a great statistical relationship found between the sales of video cassette recorders and the incidence of AIDS. A wonderful statistical relationship, and if you wonder about its plausibility, what are the people doing while they are watching the VCR's?

Mr. ROSE. How is a 90 percent confidence interval compatible with a one-tailed test?

Dr. FEINSTEIN. In the usual statistical reasoning, we start with the idea of one of those Gaussian bell-shaped curves. We then say that the inner 95 percent of data under that curve is what we are going to call customary, usual, expected. The outer 5 percent of data, which is distributed with 2.5 percent at the high end and 2.5 percent at the low end, becomes the unusuals, the abnormalities, the results that we will reject as not being compatible with the idea that they all come from the main distribution. That is a 95 percent two-tail approach because you are looking at the two tails, one on either side.

When you switch to a one-tailed 90 percent approach, you are saying "I don't care about what is going on down here at the low end or else I don't care what is going on at the high end. I am putting all of my focus at one end of the data." So you take that little 2.5 percent down there and shift it over here. When you get through all the math, you really have a 90 percent level even though you can then say, in the particular form of the statistical catechism, "I am still using 95 percent reasoning, but focusing it all on one side."

Mr. ROSE. EPA guidelines for carcinogen risk assessment require there be sufficient epidemiologic data before a substance can be classified as a group A carcinogen. We gather that at least one group within EPA believed that the ETS epidemiologic data was not sufficient to make such a claim yet Drs. Baird and Farland have today represented that the data is sufficient.

Who is right? Is the data sufficient to classify ETS as a known human carcinogen?

Dr. FEINSTEIN. In terms of who is right between the two factions that seem to be disagreeing within the EPA, I would not want to say. I have not read what was stated by the folks in Cincinnati. I don't know what rebuttals were made by the other EPA group, which I assume is somewhere in the Washington area. I would not want to get involved in that, sir.

Mr. ROSE. OK.

EPA has suggested that whether or not the majority of the ETS studies are statistically significant, it can use a "weight of evidence" approach to its carcinogen classification. It seems to some of us that we cannot allow an Agency to have guidelines for carcinogen classification that allow unlimited flexibility on how they judge whether a substance is a carcinogen or not.

What is your opinion of this "weight of evidence" position?

Dr. FEINSTEIN. Well, I don't want to get into the issue of what kinds of guidelines should be imposed on the Agency by legislation or whatever. This is an issue I would prefer to avoid since I think it is extremely difficult to try to legislate science. However, I do think that the statement made in the so-called Bradford Hill criteria and later used in the so-called Surgeon General's criteria in 1964, about demanding consistency in the results is a reasonably good demand. When you have so many studies going inconsistently in different directions, and furthermore not having highly elevated risk ratios, I think that both of those requirements of the Surgeon General and Bradford Hill criteria were pretty good demands. I would not want to see them countermanded by some kind of mathematical manipulation called "weight of evidence."

Mr. ROSE. We have heard that some of EPA's own scientists were fairly critical of the meta-analysis approach, but Dr. Farland has stated this is an example of how EPA will carry out risk assessment in the future. What is your opinion of the meta-analysis with low-risk observational studies and was EPA right to use this approach in the risk assessment? Is it right to suggest that meta-analysis should be used in the future?

I gather from what you just said that there is a need for a certain consistency here whatever approach is followed.

Dr. FEINSTEIN. As you know, Congressman, we all do things at times to be loyal. I strongly suspect that someone at EPA probably set some sort of policy, and said we would like to get the evidence to prove this point. I would guess the folks working at EPA were then loyally trying to do their best to satisfy and comply with the goals of the people that they were working under.

As a general principle for future activities, I would hope that if meta-analyses are to be done, that the material that becomes the constituents of the meta-analysis would be scrutinized with far more immaculate care than was used for the information that the EPA pooled.

Mr. ROSE. I would yield to Congressman Baesler for questions.

Mr. BAESLER. Thank you, Mr. Chairman.

I want to make sure I understood—Dr. Feinstein I believe from your slides the 1964 standards that were set out by the Surgeon General talking about little or no contradictions, talking about a high relative risk ratio and your word was preferably above three——

Dr. FEINSTEIN. Sir, the preferably above three was not in the Surgeon General's report. Their term was "strength of the association." The "preferably above three" was a type of exigetical commentary created in later years.

Mr. BAESLER. You think that commentary is correct though?

Dr. FEINSTEIN. I think it is a very useful guide, Congressman.

Mr. BAESLER. Further you talked about that in general when you are doing studies or research and you have made a distinction between editorializing and researching because I think you classified this as editorializing somebody else's research that you felt that from what you have heard today and from review of the report that the EPA study, No. 1, probably had a little bit more than few or no contradictions.

Dr. FEINSTEIN. Would you say that again?

Mr. BAESLER. That you felt that the EPA study as relates to ETS suggested a little more than a few contradictions?

Dr. FEINSTEIN. No. What I said was that when EPA combined the studies into one chowder, they combined studies that had contradictions.

Mr. BAESLER. I understand that. That is exactly right because they were different type studies and they didn't use the same basis of research. It wasn't indicated they did or they did not, but you thought it was important—but that you felt that the, when you had the chart about the different countries, the highest relative risk was 2.51?

Dr. FEINSTEIN. In the various countries, the highest per country was two. In the individual component studies, the highest was 2.5.

Mr. BAESLER. And that two compares to what we are talking about, the two or three being the high relative risk. Those are the two numbers I am comparing. I am not in the scientific community. Am I comparing apples to apples there?

When you said after the Surgeon General study—what is generally accepted as a good standard——

Dr. FEINSTEIN. I think what a lot of people have said was if the relative risk is below two, we are not even going to regard the study as a candidate for supporting the idea of risk.

Mr. BAESLER. I got you.

Mr. FEINSTEIN. Preferably it ought to be above three. In the zone between two and three there is the room for individual judgment.

Mr. BAESLER. That is all I have.

Mr. ROSE. Thank you very much. We appreciate your being here.

Is there anything you would like to add to what you have said or is there any comment you would like to make about which we haven't asked you a question?

Dr. FEINSTEIN. Not really. I thank you for the adventure. I have managed to go through many years doing research; but this is the first time I have ever been before a congressional committee. It is a very instructive experience. You should charge tuition.

Mr. ROSE. Thank you very much. We will excuse you at this time. You are welcome to stay as long as you would like.

Thank you, Doctor.

Dr. Guerin, thank you. I understand that you were one of the authors of a recent monograph that considered the chemistry and composition of ETS. The EPA's ETS risk assessment of environmental tobacco smoke considers that ETS can be classified as a group A carcinogen solely on the basis of similarities with mainstream smoke.

Could you list for us the differences between active smoking and exposure to ETS?

Mr. GUERIN. There are major differences. In terms of exposure to ETS versus active smoking, the principal differences are in the way that the smoke is inhaled. In the case of passive smoking, it is inhaled under normal inhalation conditions and in the case of active smoking, it is a matter of drawing the smoke into the mouth and taking a deep inhalation.

The pattern is different. The mainstream smoke is much more concentrated. Typically, chemicals in mainstream smoke are present in concentrations 100,000 to 1 million times higher than is encountered in passive smoke. One other possible important difference is that there are short-lived species present in mainstream smoke that are in all probability not present in environmental tobacco smoke.

Some people have postulated those kinds of constituents might contribute to lung cancer in active smokers. So there is a major difference between active smoking and passive smoking.

Mr. ROSE. I gather that the 1986 National Academy of Sciences' report on ETS listed criteria necessary for the assignment of a proper marker of ETS exposure. What were those criteria?

Mr. GUERIN. I don't recall those criteria that were used at that time.

Mr. ROSE. Do you believe that nicotine and the biomarker cotinine are adequate markers?

Mr. GUERIN. They are useful markers, but they are not adequate markers. The reason is that nicotine behaves differently in the environment than other constituents of tobacco smoke and particularly those constituents which are at least suspect to be important for biological impact. But it is the most commonly used indicator of today and probably will continue to be used for some time.

Mr. ROSE. EPA used studies that quantified very low levels of cotinine in body fluids to determine the amounts of exposure to be expected in women not married to smokers.

Is the measure of cotinine at very low levels reliable?

Mr. GUERIN. No. There are many difficulties in determining cotinine at very low levels and with generating results with sufficient confidence.

Mr. ROSE. Risk assessments are very dependent upon having good exposure data.

Do you believe that there is sufficient existing data to accurately characterize the U.S. population's exposure to ETS?

Mr. GUERIN. I do not. I think this is one of the more important needs in this area in terms of being able to establish the population risk and information is required both on the quantities of ETS constituents that the individuals are exposed to and cotinine levels for comparison but adequate data does not exist today.

Mr. ROSE. You have been very helpful. Thank you for being here, sir. We appreciate your testimony and the questions you have answered for us. We will excuse you at this time. You are welcome to stay.

The third panel is Dr. Douglas Dockery, associate professor of environmental epidemiology, Harvard School of Public Health, Boston, Massachusetts, representing the American Lung Association; Dr. Alfred Munzer, president of the American Lung Association, Washington, DC; Dr. Maurice LeVois, principal scientist, Environ-

mental Health Resources, Mill Valley, California, representing the Tobacco Institute, Washington, DC; and Dr. Gori, principal scientist, the Health Policy Center, Bethesda, Maryland, representing the Tobacco Institute, Washington, DC.

All these gentlemen can come up together.

Dr. Dockery, please proceed.

Mr. DOCKERY. If it is OK, I will defer to Dr. Munzer.

Mr. ROSE. That will be fine.

STATEMENT OF ALFRED MUNZER, M.D., PRESIDENT, AMERICAN LUNG ASSOCIATION, DIRECTOR, CRITICAL CARE, AND CODIRECTOR, PULMONARY MEDICINE, WASHINGTON ADVENTIST HOSPITAL, ON BEHALF OF THE COALITION ON SMOKING OR HEALTH

Dr. MUNZER. Mr. Chairman and members of the subcommittee, I am Dr. Alfred Munzer, president of the American Lung Association, and I am also director of critical care and codirector of pulmonary medicine at the Washington Adventist Hospital in Takoma Park, Maryland, where I specialize in the treatment of diseases of the lung. That means that 80 percent of the patients I treat have diseases directly attributable to smoking.

Twenty years ago I decided that there had to be a better way to fight lung disease due to smoking than tethering one patient with emphysema after another to oxygen, or having nothing to give to the family of someone dying of lung cancer but some comfort. That is when I became a volunteer for the American Lung Association. And the better way that I alluded to is the work of the American Lung Association, the American Cancer Society, and the American Heart Association united as the Coalition on Smoking Or Health on whose behalf I am honored to speak today.

The coalition was founded in 1982 and has been successful in such projects as banning smoking on domestic airline flights, revising warning labels on cigarette packages, and obtaining warning labels on smokeless tobacco products.

It has been estimated that by the year 2000, the antismoking movement will have saved 3 million lives, but tobacco continues to be a major public health problem and still claims 487,000 deaths annually in the United States and 3 million deaths worldwide. And saddest of all, every day 3,000 children are enticed to start smoking by unscrupulous advertising.

Over the past decade, we have learned that tobacco smoke is not only harmful to the smoker, but also to the nonsmoker exposed to secondhand or environmental tobacco smoke.

I am pleased to appear today to discuss the Environmental Protection Agency's risk assessment report, "Respiratory Health Effects of Passive Smoking." The EPA did not act in isolation and it was not the first to reach the scientific conclusions contained in the report. It followed a 1972 report of the Surgeon General, a 1982 report of the Surgeon General, a 1986 report of the National Academy of Sciences, a 1986 report of the Surgeon General, again, and a 1986 report by the prestigious International Agency for Research on Cancer and a 1991 bulletin of the National Institute for Occupational Safety and Health.

The EPA's independent risk assessment not only supported the findings of these early reports with respect to lung cancer, but also added an exhaustive review of the health effects of environmental tobacco smoke on children.

Although the tobacco industry has tried to refute the findings with respect to cancer in adults, the results concerning respiratory disease in children have not received such attention.

Let me restate these effects of environmental tobacco smoke for the record: 8,000 to 26,000 cases of childhood asthma per year; 200,000 to 1 million children already diagnosed with asthma who have a significant worsening of their shortness of breath and wheezing; 150,000 to 300,000 cases of pneumonia and bronchitis in young children captive to the environmental tobacco smoke generated by adults.

This in turn has resulted in 7,500 to 15,000 hospitalizations in these young children annually at a dollar cost of $45 million to $68 million, but at incalculable psychological cost.

Long before the EPA reached its conclusion that environmental tobacco smoke is a group A known human carcinogen, the scientific and medical communities and the general public had come to a consensus that environmental tobacco smoke causes disease. The question may in fact be asked what took the EPA so long?

Today's hearing focuses on the false tobacco industry-concocted controversy about the risks of exposure to environmental tobacco smoke. The controversy has been generated by an industry that still denies that active direct smoking kills in spite of 50,000 studies to the contrary.

Today's attacks on the integrity of the EPA parallel the charges leveled against the Surgeon General's report on smoking and health since the initial report was published in 1964. The tobacco industry has constructed its campaign of controversy on themes of poor science with questions about statistical significance, meta-analysis, confidence intervals, use of the EPA's cancer guidelines, and so forth.

Dr. Dockery will discuss some of the methodological issues raised about the report. To me as a practicing physician what we are quibbling about is the temperature at which we withdraw our hand from a burning stove.

I quote from then Health, Education, and Welfare Secretary Califano's preface to the 1979 Surgeon General's report on smoking and health: "In truth, the attack upon the scientific and medical evidence about smoking is little more than an attack upon the science itself: An attack upon the epidemiological, clinical, and experimental research disciplines upon which these conclusions are based. Like every attack upon science by vested interests, from Aristotle's day to Galileo's to our own, these attacks collapse of their own weight."

Mr. Chairman, in spite of the tobacco industry's campaign to create controversy where there is none, the American public has come to understand that environmental tobacco smoke is harmful.

In a poll conducted by the Gallup organization for the American Lung Association in 1992, 9 in 10 adults knew that environmental tobacco smoke is harmful to infants and young children, pregnant women, and older healthy adults. Even 8 in 10 smokers knew that

environmental tobacco smoke was dangerous for those around them. That is why cities in your own North Carolina like Chapel Hill, Greensboro, and Raleigh and counties like New Hanover and Wake, like scores of other localities around the country have enacted ordinances to control smoking in public places.

In summary, given the accepted consensus in the medical, scientific, and public health communities about the risks of environmental tobacco smoke and the growing public awareness of these risks, change is inevitable for those who grow tobacco. Everyone would be better served if we focused on how to best manage that change rather than continue to deny the health hazards of tobacco use.

Mr. Chairman, you have long been a champion of the family farmer. We want to offer our support for reasonable measures designed to assist the family tobacco farmer during the ongoing transition to nontobacco crops. The coalition has offered to participate in such efforts before and we do so again sincerely.

Thank you.

[The prepared statement of Dr. Munzer appears at the conclusion of the hearing.]

Mr. ROSE. Thank you very much.

You are obviously and certainly have a broad view of this entire problem. I have tried today to focus our attention on whether or not, and I look forward to hearing what Dr. Dockery will say, to find out whether or not there is valid scientific basis for these conclusions.

You have already enumerated the results which have flowed from this conclusion, the counties that have enacted smoking bans. You pointed out that 9 out of 10 smokers feel or believe that the smoke is harmful. I agree with you that that is probably a rather widely held public sentiment, but what I strenuously object to is an Agency like the EPA reaching that conclusion based on the studies that they had before.

When I heard of the result, having been interested in these studies many years ago—I haven't had that much time to focus on them lately—I said there is a new research project that has come up. Lo and behold, it was a new way of looking at 30 older tests with many still ongoing.

Don't you think—well, I think—I am not going to draw you into that—I think that the better way would have been for a properly done EPA, U.S. Government-sponsored protocol open for everybody to look at kinds of test on many subjects. I am proud of your being here. You are obviously a very eloquent and knowledgeable spokesman for the American Lung Association.

I buried two of my closest friends within the last 6 weeks from emphysema, one who carried a pure oxygen source with him every day in his pickup truck, couldn't take the pain any longer and one morning got up and attempted to kill himself, but was unsuccessful and died an agonizing death in the hospital.

He was a smoker for many years and he felt he knew where his emphysema had come from. I am not arguing about that. I don't smoke and I don't want people close to me that I care for personally to become smokers. But that is a choice that the public is free to make. I think we damage a great many things when we tamper

with the science or when we let questionable science dictate the outcome of a policy statement as strong as the one that was issued by the EPA and the results were inevitable.

The results being that they were interpreted by people who are totally opposed to any smoking anywhere, they were interpreted to be a mandate to State and local governments to pass these ordinances and to make these things happen, and political objectives achieved. In your heart, I am sure everybody feels good about the result.

You are happy with the EPA report, but is there an adequate confidence level in the statistical significance of what was presented? I think when you compare the Surgeon General's report in the 1960's to this report, I have to conclude there was some straining to come up with the result. I appreciate your position, and I am looking for alternative ways for my farmers to make a living, but the practical matter is as long as it is legal to grow, to make and sell cigarettes in America, why should they be told that they must stop growing tobacco?

The companies will smile all the way to the bank as they bring in 10 times cheaper tobacco from Africa or South America and the product will continue to be sold. So that is sort of the basis of my politics in this; but thank you for your comments and opinions.

Mr. Baesler.

Mr. BAESLER. I would like to follow up. I think without question, nobody would suggest that the predominant people in the country oppose smoking. Without question, nobody would suggest that the politically correct conclusion from the EPA was had. Without question, nobody would say that the villain on Capitol Hill and agricultural products is tobacco.

I haven't been here but 6 months and I happen to be the only burley producer in Congress, the only one that raises it himself. I suppose coming from this issue, you sat through all the testimony. You heard the EPA talk and then you heard a doctor from Yale talk.

I think tobacco farmers, even though we are the scourge of the Earth in most of the world except in Kentucky, North Carolina, and other places, I think those of us who raise it, those of us in the communities who depend on it—50 percent of the income in Kentucky in agriculture is tobacco.

I appreciate your offer to help us, but you have to tell me how they are going to help me economically and how they are going to help me change the whole culture of 150 years. I am willing to listen. All of us we think deserve, even though we are on the politically incorrect side, everybody is going to jump now and say, "You are wrong."

Even though we are the politically incorrect side, we deserve to have results that affect us, even though we are the minority, to be results based on sound information or accepted principles.

I am not a scientist, but even my little review today, when the fellow from Yale can talk about all the accepted processes that happen and they are directly in conflict with what we heard 2 hours before, all we are asking is this. If you are going to take the next step, which is to ultimately get the goal you want and most people in the country would like to have, do away with tobacco, then make

sure you take that step based on information that is derived fairly and openly. That is all we are asking.

The hearing today is to question that. It is not to question whether you are politically correct or we are not. I am not naive—if we take a vote we lose. I think we deserve that much like any other group deserves as much; if their product is going to be determined something that should be forbidden, they deserve to make sure the evidence used is correct and not start with the principle "I know I am right so nobody is going to object to my methods because my conclusion is going to be so well accepted."

If we let that process proceed without challenge, what product is next? I don't know. What minority product is next to be on the hit list?

We have always had a question about the millions we have spent on asbestos removal. All we are asking and nobody is ever going to argue about what you said about it is going to kill people and it is bad. We know that. But even that indicates, even though we are the lowest scourge of the Earth, we deserve to make sure before you put the final nail into us—not you but society—puts the final nail into us, we deserve to be assured that it was fairly assessed according to standards that were acceptable in all the communities and it was not predetermined because we are not politically correct.

My biggest concern today is to watch the standards of 1964 or whatever it was and how they didn't apply the same they applied now. A new study might say the same thing but if a new study came out, the same thing with less questions, you wouldn't hear anything from tobacco farmers.

We don't happen to think that is the biggest threat in our life. We got a few others today. But we do think, even though we are not accepted, we deserve to be treated scientifically correct and deserve to be treated scientifically—with established science. And just don't pick on—not you but the country—don't pick on us scientifically because you don't like us.

Mr. ROSE. We thank the gentleman for his comments.

Dr. Dockery, we will be glad to hear from you, but, Dr. Munzer, if you feel you would like to make a final statement we would be glad to listen.

Dr. MUNZER. The only point I would like to address is that the principal issue is not one of political correctness but one of public health. I am not an epidemiologist, but I did read this report. As a practicing physician, just someone who has gone through medical school, I believe that the conclusions reached by the EPA were reached very carefully.

There may be some scientists, physicians who will differ about some of the methodologies used by the Environmental Protection Agency, but that is always the case in the scientific community.

I believe that the evidence cited by the Environmental Protection Agency is more than sufficient for it to have reached its conclusions.

Mr. ROSE. Dr. Dockery.

STATEMENT OF DOUGLAS W. DOCKERY, ASSOCIATE PROFESSOR, ENVIRONMENTAL EPIDEMIOLOGY, HARVARD SCHOOL OF PUBLIC HEALTH, ON BEHALF OF THE COALITION ON SMOKING OR HEALTH.

Mr. DOCKERY. Mr. Chairman, thank you for the invitation to come down and speak to you today. I welcome the opportunity and look forward——

Mr. ROSE. Can I make a suggestion that we receive your whole testimony in the record? It will be printed in full, and you kind of give us a summary of the high points you would like us to have.

Mr. DOCKERY. I wasn't going to read my testimony. I assumed that would be in the record. I would like to make just a couple of additional comments.

Mr. ROSE. Certainly.

Mr. DOCKERY. Mr. Chairman, I am Douglas Dockery. I am an associate professor of epidemiology at Harvard School of Public Health, and I have had an interest in this area for many years.

I wanted to speak today on the scientific methods that were used, the scientific standards that were applied, some of the issues raised by Mr. Bayard in his comments most recently.

To me, we are not talking about new evidence, as you suggested, Mr. Rose. This is old evidence that tobacco smoke is harmful. This is not the application of new methods being applied in this particular case.

As Dr. Munzer pointed out, these associations have been shown previously in the 1986 Surgeon General's report, in the 1986 National Research Council report from the National Academy of Sciences, in the 1986 IARP report from the World Health Organization and, most recently, by the outside scientists who reviewed the work of the EPA, the compilation done by EPA in 1992 who found environmental tobacco smoke to be a carcinogen.

Now, there is plenty of evidence to suggest that that is true. As you have suggested, it is very clear that tobacco smoke is a cause of lung cancer in active smokers, and there is no reason to believe that it should act differently in people exposed at much lower levels to environmental tobacco smoke. And based on that evidence alone it is sufficient, using the same criteria that have been applied to other class A carcinogens by the EPA, to define environmental tobacco smoke as a carcinogen.

But we have the luxury in this case of having a wealth of data showing increased risk of lung cancer among people environmentally exposed to tobacco smoke. That is where the debate has been focused today, on the details and nitpicking of these arguments. But if we step back from this, the weight of the evidence, even without the meta-analysis, clearly would be sufficient to declare environmental tobacco smoke as a class A carcinogen.

My colleague, Dr. Feinstein, has made some comments suggesting that these studies do not meet the accepted criteria put forward back in the early 1960's by Bradford Hill that were restated by the Surgeon General in 1964 and have really been the basis of defining causality ever since.

In my testimony before the Science Advisory Board, I went through the 10 criteria proposed by Bradford Hill and showed how

those were applicable to the specific case of environmental tobacco smoke.

Mr. ROSE. Could you give us a copy of that for our record?

Mr. DOCKERY. I would be happy to. I will send an addendum to my prepared statement.

Mr. ROSE. I mean, the comparison, how you reached the conclusion that the criteria applied to environmental tobacco smoke.

Mr. DOCKERY. I would agree with Professor Feinstein that two of the most important criteria are consistency and the strength of the association.

I disagree with him in that where he sees inconsistency in these data I see remarkable consistency. We have 32 studies that have been discussed today, and all but one of those are consistent with an excess risk of lung cancer associated with environmental tobacco smoke. That is using the 90 percent confidence interval so that 95 percent confidence intervals are what everyone used in this case. They are all consistent with a positive association.

We have no reason to believe that tobacco smoke is beneficial for you or would be beneficial in reducing the risk of lung cancer.

Mr. ROSE. It was Robert Kennedy who said, some people see things as they are and say why? I see things as they could be and say why not?

Why don't we agree that there is a different point of view, that are both valid in interpreting the same data?

Mr. DOCKERY. I do not question that other reviewers and scientists in looking at this data may come to different conclusions in EPA than I have.

Mr. ROSE. Isn't this data pretty close to the line?

I am not arguing with you about the direct smoking matter. But when you get down to a heavy reliance on a study that shows 1.04, if they use a one-tailed study, less than one if you use a two-tailed study, isn't that cutting it pretty close, Dr. Dockery?

Mr. DOCKERY. We are not talking about whether these are real effects based on statistical significance. Statistical significance is not a measure of association in these. We are finding positive associations in all these studies.

Mr. ROSE. What is?

Mr. DOCKERY. What is?

Mr. ROSE. Yes.

Mr. DOCKERY. What is the basis on which we come to the decision there is causality in this case?

Mr. ROSE. Yes.

Mr. DOCKERY. That we have the evidence to clearly show that tobacco smoke is the cause of lung cancer.

Mr. ROSE. To what?

Mr. DOCKERY. We have very clear evidence that tobacco smoke is the cause of lung cancer, that sidestream tobacco smoke contains the same carcinogenic chemicals found in active smoking, that people are exposed in the environment to tobacco smoke with those same carcinogenic chemicals, and that we can demonstrate very strongly with epidemiology, despite all the problems of this blunt instrument, that there is an excess risk and statistically significant increased risk associated with environmental tobacco smoke.

Mr. ROSE. Is chlorine carcinogenic?

Mr. DOCKERY. I am not sure. I was not prepared to answer that question today. It is certainly not listed as a class A carcinogen. It has been postulated that it contributes to cancer in the water chlorination processes. If that is the line of reasoning you would like to pursue, I would be happy to discuss that.

Mr. ROSE. Well, since you don't know about that I won't ask you where you shower.

We will continue with the hearing.

We need to vote, and we will be right back. Please excuse us for a few minutes.

[Recess taken.]

Mr. BAESLER [assuming chair]. If we can, we are going to get started. Chairman Rose is going to be tied up for a few minutes, he thinks.

Dr. Dockery, we are going to resume with you. I don't know whether you were through your statement or not. If you were not, go on.

Mr. DOCKERY. Actually I didn't finish my statement, sir. Thank you for the opportunity.

Let me find out where I was.

We had talked about the consistency of the associations, and I think there is—at least in my reading of these studies, there is strong consistency. I do not question that other reviewers would disagree with that.

The other item that Dr. Feinstein brought up was the strength of the association. Now, he has focused on the strength of the association for environmental tobacco smoke, but I don't think that is the issue here. The issue is what is the strength of association for tobacco smoke.

And, as Dr. Feinstein showed in his slide, the relative risk for tobacco smoke for heavy smokers is over 20. Those are huge relative risks, and it should not be surprising that we find increased relative risk associated with small exposures to environmental tobacco smoke. So it is simply a question of how you interpret the data.

In fact, if you go back to the Bradford Hill article, the original, the example he used for defining causality was tobacco smoke, and he went through all the criteria to use that as the example.

In 1961, I think, when that article was published, it was true, and it is still true today. Lung cancer is caused by tobacco smoke. We should not be surprised that we are finding effects from environmental exposures at this time. We have certainly become much more sophisticated in our epidemiology. We have much greater power in our epidemiologic studies to detect these effects, and it is because of that increased power and increased sophistication that we can see these effects at very low exposures.

But that is not the criteria that should be used in defining whether tobacco smoke is an environmental carcinogen.

I would say, just to sum up here, that my reading of this document is that, realistically and objectively, it provides an unbiased review of the data. The meta-analysis, in particular, is an important new technique, at least in rulemaking. And certainly it isn't new in terms of epidemiology, but it is a new application, and it provides scientific rigor and objective methods for quantifying the

weight of evidence. It provides specific rules that are used in specifying what the weight of the evidence is.

This is one thing, Mr. Baesler, you have requested, that the rules be set down, and this is what the meta-analysis does. It is not a black box, not some black magic. It is actually very simple weighting of the evidence here both pro and con. I think it really is a major step forward in rulemaking, and I really support the EPA in its use.

I am sure you have a lot of questions for me so why don't I take those?

[The prepared statement of Mr. Dockery appears at the conclusion of the hearing.]

Mr. BAESLER. I don't really, but I have a couple. I think we have Yale on one side, Harvard on the other.

Mr. DOCKERY. That is often the case.

Mr. BAESLER. Now in the middle is the poor tobacco farmer way out in the boonies somewhere, and we wonder if we are getting a fair shot. And then we got Yale saying maybe not. Harvard says you are. So we have to be a little confused.

I reckon my concern is that—and I think Chairman Rose indicated before he left—that the conclusion could have been reached, but it is not going to help you any—I am talking about the report. It is borderline.

Chairman Rose asked this before he left. I believe it is borderline, and we could go either way. The EPA chose the way it thought it should go and which you support. I understand that. It is borderline, but does borderline constitute it saying it causes 3,000 deaths every year? They didn't say it is harmful but that it is causing 3,000 deaths minimum a year. So that is what I think has us concerned, and I am sure one side could say yes and the other side say no.

But do you think there is a danger in any of these type studies if we have a certain conclusion we tried to reach and we know we want to reach—do you think that has a long-range danger for the scientific community generally if we use the methodology of let's find what we want? We know what the conclusion is. How do we get to it? Isn't that a little dangerous?

Mr. DOCKERY. I think the danger is using the methods used in the past to review the data. In my estimation, the methods that have been set forth in this document and the criteria that have been set and the objective weighting scheme used in the meta-analysis provides us with the scientific rigor we need in doing this type of evaluation.

Now, these were weak effects. There is no denying that because these are very low exposures.

But the question you raised about the 3,000 deaths, that is not a statistical question here. That is based on the evidence from the data. The 3,000 deaths is not based on a .05 or 90 percent confidence interval or 95 percent CI. That is the best estimate that EPA could make from the available data.

And about that 3,000 deaths, there is also a confidence interval, and I don't happen to know what it was offhand, but maybe it went from zero to 6,000 deaths or something. But there is some confidence we have about that data, also.

This issue of confidence is very important here. We are talking about how much confidence do we have in these results, and it is exactly how it sounds. How much confidence do you have in this?

If I told you as a tobacco farmer that you used a certain chemical in your field and it improved your yield and it was very expensive and had very serious implications economically for you, you would ask me how confident you are in that.

If I said, well, I am—no, I am 95 percent confident you would probably say that sounds pretty good to me. If I said 90 percent—I am 90 percent confident, I would expect you would say that sounds pretty good to me, also.

But if I go from 95 percent confident based on the statistical test to 90 percent confident I am not saying that it is not true. I am just saying that there is just this tiny little bit of less confidence that I have. But I am still nine-tenths confident that this is the association.

We have been arguing—not we——

Mr. BAESLER. Not we, no.

Mr. DOCKERY. The other speakers have been arguing about this 95 percent confidence value. For the EPA estimate of 1.19 for the U.S. studies which Mr. Rose referred to, it had a lower bound based on the 90 percent confidence interval of 1.04.

I just sat here with my calculator and, at least from my calculation, if you use a 95 percent confidence interval the lower bound is 1.01. It is still above the know. We are still seeing a positive effect.

My own calculations, using the same data which are in my prepared testimony, suggests that there is very high statistical power here, that these results all achieve statistical significance at the 5 percent level or whatever you want to use here. We are just not——

Mr. BAESLER. I understand. That is one of my concerns that we are taking—obviously, only the scientific community understands all the figures you are talking about.

But with the difference of interpretation, with such a small room for error, when we finally reach that conclusion it could have a devastating effect. To me, the uncertainty, the inconclusiveness, whatever it is we have, that is what has caused this whole clouded picture. We would all have to be at the table trying to defend it if it were certain. You know that.

Let's see what the other folks have to say and——

Mr. DOCKERY. Can I just respond to that statement, sir?

Mr. BAESLER. Certainly.

Mr. DOCKERY. We are talking about severe economic effects, also, but we are talking about severe public health effects also—but this is a very big public health issue.

Mr. BAESLER. And we are trying to distinguish between the use and the other. It is a big public health issue, I understand. It is a big economic issue. Big public health issue. I often wish we had the same discussions about Mexican beer, but we never do. I often wonder about that.

I got 40,000-some people killed involuntarily. But that is why I get back to the point of what you want to talk about.

If you have to go, Dr. Dockery, fine. If you want to stay and hear the other gentlemen, they will not agree with everything you said.

Mr. DOCKERY. I might expect so.

Mr. BAESLER. You are welcome to go if you have other commitments.

Dr. Gori.

STATEMENT OF GIO BATTA GORI, PRINCIPAL SCIENTIST, HEALTH POLICY CENTER, ON BEHALF OF THE TOBACCO INSTITUTE

Mr. GORI. Thank you, Mr. Chairman.

I am Gio Gori, a toxicologist with training in epidemiology, and I am a long-time student of risk assessment. I am president of the International Society for Toxicology and Pharmacology and a fellow of the Academy of Toxicological Science.

I am here because the Tobacco Institute asked me to review the scientific basis for the EPA report on environmental tobacco smoke.

We have heard the EPA report relies mainly on the claim that environmental tobacco smoke is equivalent to the smoke that smokers inhale. This is the fundamental justification of the EPA report.

I would like to read from the report itself. On chapter 2, page 9, the report indicates that, in fact, the similarity of environmental tobacco smoke and mainstream smoke is sufficient, "To establish the weight of evidence for classifying environmental tobacco smoke as a group A carcinogen under EPA guidelines."

However, the same report, chapter 6, page 6, lists all the differences of mainstream smoke and sidestream smoke. They differ in relative composition of components identified in tobacco smoke and in physical and chemical properties in general. The size distribution of particulates in mainstream and sidestream smoke are affected by the concentration of the vapor phase and subsequent differences as sidestream and mainstream environmental tobacco smoke age.

Active and passive smoking differ in characteristics of intake. For example, intermittent inhalation in contrast to deep inhalation which may affect the systemic deposition of tobacco components.

On the basis of these differences, the report concludes that the implication that both carry the same lung cancer risk is not tenable.

It is clear to me that the EPA itself is not very sure about the similarity or the purported equality of mainstream and sidestream smoke.

Now, about the consistency of the data, we have 16 studies of exposure in the workplace that show no combined elevation of risk. Many studies actually show decreased risk. Twenty-three studies of persons exposed to ETS since childhood show no increase of risk. As a matter of fact, many imply a decreased risk. And here I don't want to be interpreted to suggest that we should wean our children on cigars. The fact is that the data go on both sides of the equation.

Even the 11 studies used by EPA to calculate the combined risk of nonsmoking wives of smokers are conflicting. And, of course, EPA ignored the data from some of the later studies, namely the Stockwell study and Brownson study.

So consistency here is in the eyes of the beholder, I believe. Yet anybody who looks at the data themselves will have to reach the conclusion that the studies certainly are not consistent because results fall on both sides of the fence.

We have heard about the figure of 3,000 lung cancer cases a year being a midpoint estimate and that the midpoint estimate would not change if we change statistical intervals. I think that we have beaten to death the issue of statistical intervals today, and I am not going to dwell on that issue again. I am just trying to tell you that a simple consideration of biases and confounders will shift the midpoint estimate regardless of the confidence intervals that we can adopt.

For instance, there is plenty of evidence in the scientific literature that at least 5 percent of those who declare themselves as being nonsmokers are in reality smokers.

This bias was acknowledged by the Environmental Protection Agency, but they adopted only a 1 percent correction factor. If they adopted even a 3 percent correction factor, the midpoint estimate would disappear. So this is not a question of confidence intervals but is actually a question of moving the midpoint estimate.

Additional movements of midpoint estimates toward zero, toward 1 if you wish, will come out if the Agency considered more carefully or demanded more insistently clarification about confounders like diet, exercise, socioeconomic status and so on. All these issues were rather glossed over by the Agency and would all provide inference that would not support EPA's conclusions.

Now, about the comments of the International Agency for Research on Cancer, described here as a most prestigious international body in public health. I just want to read you what the International Agency said: "Substantial difficulties in the determination of passive exposure to tobacco smoke and to other possible risk factors are present in the epidemiologic studies. The resulting errors could arguably have artificially depressed or raised estimated risks and, as a consequence, each is compatible either with an increase or with an absence of risk."

As a matter of fact, they are also compatible with a decrease of risk.

Despite this declaration the Agency went on to say that: "Based on prudence, environmental tobacco smoke is likely to be human lung carcinogen." Yet, on a scientific basis, their conclusion was the data are compatible either with an increase or with the absence of risk.

Now, besides the IARC, there have been comments about lung cancer and environmental tobacco smoke exposure from members of the committee that reviewed the EPA report, the advisory committee, and especially from one of the members of the committee, Dr. Jonathan Samet. In a book edited by the chairman of the committee, Dr. Morton Lippman, this is what he had to say: "The extent of the lung cancer hazard associated with involuntary smoking in the United States and in other countries remains uncertain."

The epidemiologic studies provided varying and imprecise measure of risk, and exposures have not been characterized for large and representative population samples. Nevertheless, risk estimation procedures have been used to describe the lung cancer risk

associated with involuntary smoking, but the assumptions and simplifications must be made in order to use this measure."

The EPA claims, as we have heard, to have used the weight of evidence approach. However, it is plain to me and to any unbiased observer that EPA made very selective use of available studies, emphasizing only those that support its objectives and disregarding the others.

The EPA report on environmental tobacco smoke may be an effective policy instrument, as we have heard, but EPA's claim of scientific support is grossly misrepresented.

Surely, EPA thinks that tobacco control is a legitimate public health issue, but does the end ever justify the means? Should good intentions forgive an official report that otherwise would guarantee severe censure to any individual scientist or academic institution?

Mr. Chairman, these are no trivial questions in defense of tobacco interests. They obviously reach far beyond the ETS issue. Ultimately, they will determine the credibility of science and its continuing public support and, more important, whether civic institutions deserve the public trust.

I thank you, Mr. Chairman.

[The prepared statement of Mr. Gori appears at the conclusion of the hearing.]

Mr. BAESLER. Thank you, Dr. Gori. If I understand your last statement, it is the long-range ramifications if you let public policy drive the scientific research.

Mr. GORI. Correct. I think we should worry about the future of freedom in this country, Mr. Chairman.

Mr. BAESLER. Let me ask Dr. Maurice LeVois to give his statement now.

STATEMENT OF MAURICE LeVOIS, PRINCIPAL SCIENTIST, ENVIRONMENTAL HEALTH RESOURCES, ON BEHALF OF THE TOBACCO INSTITUTE

Mr. LEVOIS. I am Maurice LeVois, and I am the principal scientist in environmental health resources in Mill Valley, California. I was former director of the agent orange research project at the Veteran's Administration here in Washington, DC and a scientist at the Centers for Disease Control.

The views I have formed are based on my own reading of this literature and represent my views and not the institute for which I presently work. But I have for sometime been following this literature. I have been commenting in writing and orally before the Science Advisory Board of the EPA, and I welcome the opportunity to again express my views.

I will try to be brief because I have already submitted in writing comments to the committee and what I have to say is different than those comments. It has to do with one of the issues that have been, I think, repeatedly misrepresented by people at this table who are not themselves epidemiologists, who do not attend the epidemiology meetings and who don't really know what is going on in this field.

That is particularly true of the EPA where there is no title epidemiology. They have dissolved or eliminated that some time ago at the recommendation of some Administrator or other and the very

few people that have training are often in remote offices. Some of the best epidemiologists in my view are in the dissenting office in Cincinnati. They are young people whom I went to graduate school with or have known over the years and have a great deal of respect for.

Let me go through a very quick explanation of where I think the field in epidemiology is with respect to the question of meta-analysis which is the central most important leg upon which the EPA risk analysis is based.

I was recently at the annual meeting of the Society for Epidemiologic Research in Keystone, Colorado, June 16 through 18 of this year, and there were discussions on the issue of the use of meta-analysis for trying to infer causation and to gain a better understanding of epidemiologic studies by pooling them.

The discussants were Drs. Sander Greenland and Diana Petitti of the University of California, and Sam Shapiro of the Sloan Epidemiology Unit, all well-known epidemiologists, and Sander Greenland certainly one of the leading methodologists and biostatisticians writing in the epidemiology journals. All three discussants agreed that meta-analysis of epidemiologic data is essentially useless as an aid to drawing causal inferences from epidemiologic studies reporting weak associations, i.e., relative risks of less than about two, because it is impossible to exclude bias and confounding as alternative explanations.

They further agreed that most meta-analyses of epidemiologic data appear to be aimed at cutting off debate and stifling further study of controversial topics rather than highlighting differences and discrepancies among the studies and seeking improved research methods.

All three discussants expressed concern that meta-analysis abuses are becoming increasingly common in epidemiology, and at the present time there has been little or no critical review of this problem.

Although the discussants were chosen in the hope that there would be a lively debate on the topic, the discussants noted themselves that their disagreements, if any existed, were largely peripheral, relating to some fine points about what role, if any, meta-analysis should play in interpreting epidemiologic results. The published abstract of Dr. Shapiro's comments entitled "Meta-Analysis, Shmeta-Analysis" indicates how negative these discussants were on this topic, and I quote from his published abstract: "In the past decade there has been an explosive growth in the application of meta-analysis to published observational data, mainly in order to confer statistical stability to relative risk estimates of low magnitude. That is below about two. In theory, systematic biases across published studies—including the selective publication of positive studies—and of shared confounding cannot be eliminated by meta-analysis. In practice, there are commonly strong grounds for inferring shared biases or confounding do, in fact, exist. Even the decision to undertake a meta-analysis may be biased. For relative risk estimates of low magnitude rendered statistically stable by meta-analysis, it still remains beyond the resolving power of nonexperimental research to distinguish between bias, confounding and causation. Additional defects of meta-analysis are esoteric im-

penetrability of the data, excathedra judgments—or no judgments at all—of the quality or validity of the individual components studies, discouragement of further research, encouragement of exaggerated claims and generation of a new Ph.D. industry. The use of meta-analysis in observational research should be abandoned."

The EPA's ETS risk assessment, based largely on meta-analysis of a collection of weak epidemiologic studies, is a striking example of the misuse of meta-analysis. Only the generation of new Ph.D.'s is lacking.

That concludes my prepared comments. But I would like to say I believe that when one considers the gulf between the meta-analysis of active smoking data and the meta-analysis of environmental tobacco smoke data you have to realize that when you are dealing with very small studies—and most of these are very small studies because by necessity they have to be—lung cancer is a rare disease in nonsmokers. When you have very small studies you are not able to stratify to control for various subgroups that may have different types of confounders such as different occupational exposures, different diets, different activity levels, and physical fitness such as exposure at the workplace because of their socioeconomic status.

There are so many things that one cannot control for in small studies that to pretend that spousal smoking is a perfectly acceptable surrogate measure for environmental tobacco smoke exposure and ignore all the potential confounders as well as the bias introduced by the fact that spouses of smokers are more likely to be former smokers themselves who are denying because of a variety of reasons that they are former or current smokers, and simply to look for more precision without demanding more validity is a misuse of meta-analysis. And I believe that that is a form of alchemy that does not produce a more valid answer to the question does environmental tobacco smoke at environmental levels raise the risk of lung cancer?

It is theoretically predicted, if you use the methods that the EPA uses for doing dose response extrapolation, that there would be some increase in risk. But if you use those methods based on the active smoking epidemiology, the level of risk predicted is hundreds to thousands of times below the level reported by these epidemiology studies.

That is an inconsistency that, to my mind, has never been adequately addressed by the EPA. And I believe that it is really a reflection of the collection of biases and confounders that go along with spousal smoking definition—which is what these really are. They are not environmental tobacco smoke studies. They are studies of the risk of lung cancer in the spouses of smokers compared to the spouses of nonsmokers, and they have different risk factors all together for many other lung cancer risk factors.

That is a problem that meta-analysis cannot and will never be able to solve.

That is my prepared and unprepared comments.

[The prepared statement of Mr. LeVois appears at the conclusion of the hearing.]

Mr. BAESLER. I would like to follow up. As we had a discussion with on the confounders I believe I recall their testimony said they

did not think the concern of the confounders in this study—I forget the person's name—was relevant. Do you agree or disagree?

Mr. LEVOIS. I disagree entirely. I don't believe any of the studies. I have read them all carefully. I know most of the researchers personally. Most of them do not feel that the relevant issues about confounding and bias can even be addressed in this form of study design. You can do a better job than has been done, but I don't think that any of the studies have adequately addressed the lifestyle differences and other risk factors that go along with being the spouse of a smoker.

Mr. BAESLER. Dr. Dockery, what do you think?

We are talking about—you remember the testimony of the EPA, Dr. Fontham.

Mr. DOCKERY. The Fontham study, which I consider a premier study. That is coming forward right now.

I was very interested in your comment; as I understood it I wasn't at the SAB hearing when Dr. Fontham made her testimony, but from what you said she testified that, in fact, adjusting for these confounders in her analysis made no difference in the associations she found. If I can't take her word for the associations and lack of confounding due to nutrition and lifestyle in these data, then I am not sure where I should turn.

Mr. BAESLER. It is so far back I don't know exactly what she said on that, but isn't it true that understanding the confounding information should have been taken into account in the EPA study or not?

Mr. DOCKERY. I certainly agree that confounders and potential biases here are an important question that has to be addressed.

My evaluation of the EPA is that they have done a remarkable job in responding to some of these spurious confounders—possible confounders—raised by the tobacco interests. In particular, the purpose of meta-analysis, in my estimation, is not to combine data to provide a reduced confidence interval or increased statistical significance, but it provides a method in which you can contrast studies with differing control of confounders and different study designs or different countries of origin and so forth.

In fact, that is exactly what was done in the EPA analysis. They did the contrasts. They looked at the studies by country of original. They looked at studies by the control of confounders. They looked at studies to evaluate whether it is possible to—whether any confounders could explain these weak associations.

In fact, the answer was no. You cannot find any evidence in any of these studies that there is a major confounder in these analyses.

That is what the EPA people testified to this morning.

Mr. BAESLER. Would you like to comment.

Mr. GORI. I have a copy of the Fontham study, Mr. Chairman, I brought it with me today. In this report it says that: "Because the magnitude of the main environmental tobacco smoke is expected to be small, it is important to take into account potential confounding factors, in effect modifying factors, in a study with sufficiently large numbers of cases and control. It is anticipated that upon completion of this study about 600 cases would have participated."

This is clearly an indication that they have not collected the necessary information about confounders yet.

This report represents findings from the ongoing study, an incomplete study, therefore, and includes the largest number of lifetime nonsmokers with lung cancer reported to date. This report was justified because of the public health importance of the issues under investigation.

Clearly, the Fontham study had not collected the necessary information for confounders when it was published.

Mr. BAESLER. I believe they further stated there was a grant given to check that part of it.

Would you like to comment, Doctor?

Mr. LEVOIS. Yes. The issue of confounding, particularly by dietary confounding, is very difficult to resolve. The National Cancer Institute has said that they believe that a third of all cancers are related to diet. It has been notoriously difficult, however, to demonstrate that because diet is so very difficult to measure over a long period of time and with the kinds of precision that are needed to find small effects.

I came from a recent toxicology forum in which Dr. Earnst Swinder, president of the American Health Foundation, said that he believed personally that dietary fat was an ubiquitous risk factor for cancer—not just lung cancer but most cancers.

This has been documented off and on both in animal toxicology and through a variety of different theoretical approaches since the 1960's; yet it has been notoriously difficult to consistently show that this is the case. But most people in the cancer epidemiology community believe it.

It is therefore not surprising that a study of environmental tobacco smoke that does a cursory job of assessing dietary habits would not be able to adjust away an effect that could be attributed to dietary causes. It is notoriously difficult to measure this, but the diets of smokers and nonsmokers are very different and on theoretical grounds, it is very likely the diets of smokers contribute to their cancers and that the diets of nonsmokers who live with smokers are similar.

So I think that there is a problem that is theoretically very plausible and persuasive to me that it is very difficult to get to the blunt instrument of epidemiology.

Mr. BAESLER. Dr. Dockery, we are not going to beat 90 and 95 percent to death anymore, but I have one question. You recently conducted a study talking about air pollution causes up to 60,000 deaths per year. Did your study use 90 percent or 95 percent confidence intervals?

Mr. DOCKERY. All our studies are reported, I think so far with 95 percent confidence intervals. That is our practice.

Mr. BAESLER. You are a recognized authority or you wouldn't be here today.

Mr. DOCKERY. I point to a greater authority than me. In this book by Ken Rothman called Modern Epidemiology, that was published in 1986, he says the level of confidence can be set at any value because it is arbitrary, but values of 95 percent, 90 percent and occasionally 80 percent are commonly used. There is certainly no standard here within the epidemiologic community on what could be used.

Mr. BAESLER. But when you are in charge, you are more comfortable with 95 percent?

Mr. DOCKERY. If I were working with a toxic agent like tobacco smoke where the evidence is clearly that there is no beneficial effect, then I would not be averse to using a one-tailed test.

Mr. BAESLER. Did you use a one-tail or two-tailed test in the study you just mentioned?

Mr. DOCKERY. I didn't specifically address that study because it hasn't been published yet.

Mr. BAESLER. I don't know how it got here, but I read it.

Mr. DOCKERY. You read the New York Times, I think. In general, we use two-tailed tests.

Mr. Baesler, all we are talking about is the size of these studies. If a large enough study is accomplished, and potentially the Fontham study when it is finally done will be large enough, they will have a much stronger statistical power to look at these associations and this whole debate might become moot then.

Mr. BAESLER. Speaking of debate, there haven't been too many studies that have created such a debate nationwide I wouldn't think. It seems to me that being the case, it probably deserves to not have a narrow scope of study or more narrow procedures or disciplines involved in the study but a broader one. That is what concerns us who are affected by it.

Dr. LeVois, we gather that the EPA decided that the study reported in 1992 by Brownson had no significant impact on the data set. Do you concur with that?

Mr. LEVOIS. I don't. What they said was they would have made the same decision regardless. That is a little different than saying it would not have had a statistically significant impact. The statistical impact is clear that if you had included that study using exactly the same rules that apply to all the others, that the confidence interval notwithstanding, the calculation of Dr. Dockery is definitely statistically nonsignificant, that is a lower confidence interval does in fact reach down to about 0.95 even if you use the 90 percent confidence interval.

Mr. BAESLER. I think we are about concluded here. From our perspective, or mine, it would seem that we have people here who—people in the field, Dr. Dockery, Dr. Gori, Dr. LeVois, others from Harvard, all over the world who disagree on the study. Some are paid by the tobacco industry, some by the Heart Association, some are paid not by anybody.

From those of us who have no knowledge scientifically but only have experienced the result of the studies from the people we represent, it would seem we maybe deserve, maybe those who have ill effects of it, maybe we all deserve to have a study that is more accepted by the scientific community. Before we determine what the results are going to be, maybe we need to have a little rehash of this because I think those of us who are affected, I feel they have taken what they want and say here it is and therefore you are going to be affected by it, and there is no agreement on the fact that the studies were conducted appropriately or like they should have been.

I think that leaves a public not part of the scientific community at a large disadvantage and I think it sets a poor precedent for

things that have happened in the past that have nothing to do with tobacco. I do think it sets a precedent of making public policy and then getting the studies to support the public policy. Whether it is tobacco, whether it is whiskey, whether it is Georgia peanuts, I think that is what concerns us who have had no knowledge of this whole process until today.

So I appreciate your coming and I appreciate your views. I am sure this is not the last we are going to hear because I understand it might be tried in a court some place.

We will hold the hearing record open for 10 days. Anybody that wants to make further reports can. This meeting is adjourned. Thank you all for coming.

[Whereupon, at 3:35 p.m., the subcommittee was adjourned, to reconvene, subject to the call of the Chair.]

[Material submitted for inclusion in the record follows:]

STATEMENT OF
WILLIAM H. FARLAND
DIRECTOR
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
ENVIRONMENTAL PROTECTION AGENCY
BEFORE THE
SUBCOMMITTEE ON SPECIALTY CROPS AND NATURAL RESOURCES
COMMITTEE ON AGRICULTURE
HOUSE OF REPRESENTATIVES

July 21, 1993

Good morning, Mr. Chairman and Members of the Subcommittee. Thank you for the opportunity to appear before you today to discuss scientific and procedural issues regarding EPA's report on passive smoking.

The U.S. Environmental Protection Agency (EPA) has published an assessment of the respiratory health risks of passive smoking (*Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders; EPA/600/6-90/006F*). The document has been prepared under the authority granted to the Administrator, including Title IV of the Superfund Amendments and Reauthorization Act of 1986 (Radon Gas and Indoor Air Quality Research), which directs EPA to conduct research and disseminate information on all aspects of indoor air quality. The report concludes that exposure to environmental tobacco smoke (ETS) -- commonly known as secondhand smoke -- is responsible for approximately 3,000 lung cancer deaths each year in nonsmoking adults in the U.S. and seriously affects the respiratory health of hundreds of thousands of children. The following testimony summarizes the development of the report, the scientific review process,

the major findings and the scientific approach. The testimony concludes with responses to tobacco industry criticisms.

Background

In recent years, comparative risk studies performed by EPA and its Science Advisory Board have consistently ranked indoor air pollution among the top five environmental risks to public health. Environmental tobacco smoke is a complex mixture of many indoor air pollutants and, given the known health impact of tobacco smoking, there has been concern that nonsmokers may also be at risk of serious health effects.

As part of its efforts to address all types of indoor air pollution, EPA's Indoor Air Division in 1988 requested that EPA's Office of Research and Development (ORD) undertake an assessment of the respiratory health effects of passive smoking. Because of both resource and time limitations, the assessment was limited to respiratory health effects, both cancer and non-cancer, rather than a broader investigation. The report was prepared by ORD's Office of Health and Environmental Assessment (OHEA), and was written with both in-house staff and outside contracting assistance.

As part of the document preparation process several levels of in-house review and sign-off were required before the report was released to the public,

either as a draft or final report. While the ETS Project Manager in OHEA is responsible for the report's overall contents and its conclusions, after his preparation and sign-off, three intermediate level sign-offs were required before submission for official Agency review. The official Agency review and sign-off authority for release of either the external review drafts or the final report was the responsibility of the Assistant Administrator for ORD, a position formerly held by Mr. Erich Bretthauer.

Before being released in draft form for public review, the passive smoking report received many internal reviews, mostly from within ORD. Various parts of it were also reviewed by selected outside experts, both from other Federal agencies and from academic institutions. Revisions incorporated the reviewers' comments wherever possible.

Public and Scientific Reviews

A first external draft of this assessment was released for public review and comment in June 1990. In December 1990, EPA's Science Advisory Board (SAB), a committee of independent outside scientists, conducted a review of the draft report and submitted its comments to the EPA Administrator in April 1991. In its comments, the SAB's Indoor Air Quality/Total Human Exposure Committee concurred with the primary findings of the report, but made a number of recommendations for strengthening it.

Incorporating recommendations from both the public and the SAB, a revised draft was transmitted to the SAB in May 1992 for a second review. Following a July 1992 meeting the SAB panel endorsed the report and its conclusions, including a unanimous endorsement of the classification of environmental tobacco smoke as a Group A (known human) carcinogen.

The EPA also received and reviewed public comments on the second draft, and integrated all appropriate material into the final risk assessment. The final report was released in January 1993, at a joint press conference held by former Administrator Reilly and former Department of Health and Human Services Secretary Sullivan.

Major Conclusions

Based on the weight of the available scientific evidence, EPA has concluded that the widespread exposure to environmental tobacco smoke in the U.S. presents a serious and substantial public health risk.

In adults:

* ETS is a human lung carcinogen, responsible for approximately 3,000 lung cancer deaths annually in U.S. nonsmokers. ETS has been classified as a known human or Group A carcinogen under EPA's carcinogen assessment guidelines. This classification is reserved for those compounds or mixtures which have the

strongest data to determine a cause - and - effect relationship, including data from human populations. Only ten other agents, including asbestos and radon, have been classified by EPA as Group A carcinogens, and ETS is the only one for which cancer has been observed at typical non-occupational environmental levels.

* ETS has subtle but significant effects on the respiratory health of nonsmokers, including coughing, phlegm production, chest discomfort, and reduced lung function.

In children:

* ETS exposure increases the risk of lower respiratory tract infections such as bronchitis and pneumonia. EPA estimates that between 150,000 and 300,000 of these cases annually in infants and young children up to 18 months of age are attributable to exposure to ETS. Of these, between 7,500 and 15,000 are estimated to result in hospitalization.

* ETS exposure increases the prevalence of fluid in the middle ear, a sign of chronic middle ear disease. Fluid in the middle ear is the major cause of hospitalization of young children for an operation in the U.S.

* ETS exposure in children irritates the upper respiratory tract and is associated with a small but significant reduction in lung function.

* ETS exposure increases the frequency of episodes and severity of symptoms in asthmatic children. The report estimates that 200,000 to 1,000,000 asthmatic children have their condition worsened by exposure to environmental tobacco smoke.

* ETS exposure is a risk factor for new cases of asthma in children who have not previously displayed symptoms.

Scientific Approach

EPA's methodology for hazard identification of health effects is based on a total weight-of-evidence approach, which encompasses evidence on exposure, physical and chemical properties, and toxicology, including animal and human studies. Because environmental tobacco smoke (ETS) contains over 4,000 individual components, including over 40 known human and animal carcinogens, examining components individually would be prohibitive. Instead, ETS was evaluated as a complex mixture. Also, the analysis focused on the respiratory system since that provided the largest database.

The methodologies used for the assessment of lung cancer and noncancer respiratory effects in the EPA report differ somewhat. First, lung cancer is only seen in adults and is thought to represent the effect of long-term exposure. The noncancer respiratory effects examined are most apparent in children, and some of

these are irritation effects associated with acute exposures. Second, for lung cancer less is known about mechanisms than is the case for some of the childhood respiratory effects, and this leads to differences in the development of the evidence. Third, because there were 30 studies on lung cancer and ETS, this database was analyzed several different ways before arriving at an overall conclusion. For the various childhood respiratory effects that were examined, there were fewer studies of any one effect and analysis was more limited.

For all effects, studies examine home smoking patterns as a surrogate for ETS exposure. The exposure surrogate in the studies of lung cancer among nonsmokers is spousal smoking patterns. For childhood respiratory effects, parental smoking is the most common surrogate, although recent studies have also shown high correlations between body metabolites of ETS and pneumonia, bronchitis, asthma, and fluid in the middle ear.

There is nearly universal exposure to ETS, which often clouds the distinction between "exposed" and "unexposed" subjects and makes any potential effects difficult to observe. To try to eliminate the effect of some of these misclassified exposures, two methods are used. For hazard identification purposes, trend analysis and analyses comparing high exposure groups with controls are conducted. For population risk estimates, a model which adjusts for background (i.e., non-home) exposures is used.

Lung Cancer

The conclusion that ETS is a human lung carcinogen is based on the total weight of the available scientific evidence. This evidence includes:

- the strong exposure-response relationships for active smoking for all 4 major lung cancer types, with no evidence of an exposure threshold;

- the chemical similarity of mainstream smoke and ETS, both of which contain over 40 carcinogens;

- supporting evidence from animal bioassays and genotoxicity studies;

- evidence of ETS exposure and uptake by nonsmokers; and

- data from 30 epidemiology studies of ETS and lung cancer from 8 different countries.

The epidemiology studies attempt to estimate the relative risk of lung cancer from actual environmental levels of ETS. Such investigations are inherently difficult for a variety of reasons, not the least of which is the fact that virtually

everyone is exposed to some level of ETS from a variety of different sources. Therefore, the studies try to compare risks in people with greater versus lesser exposures. All 30 epidemiology studies provide data on female never-smokers classified as "exposed" or "unexposed" on the basis of whether or not their husbands smoke. Although spousal smoking status is the best single measure of ETS exposure, it is a crude measure, and the studies are prone to exposure misclassification which decreases their ability to detect an increased risk if one exists. Furthermore, many of the studies are of small size and have a low statistical power to detect an increased risk.

In the EPA report, the epidemiologic data are analyzed a variety of different ways, and each analysis demonstrates an association between ETS and lung cancer. First, the studies were analyzed individually. Using the crude "exposed" versus "unexposed" measure, 24 of the 30 studies found an increased risk of lung cancer in the exposed group; nine of these were statistically significant. This proportion (9/30) of significant studies is highly unlikely to have occurred by chance (probability < one in 10 thousand). In addition, ALL 17 studies with data categorized by exposure level (i.e., amount of spousal smoking) found an increased risk of lung cancer in the highest exposure group, and 9 of the 17 were statistically significant (probability < one in 10 million), despite most having a small sample size. Examining only the highest exposure group helps to minimize exposure misclassification in the "exposed" group, since women whose spouses smoke a lot

are more likely to be exposed to substantial amounts of ETS. Finally, 10 of the 14 studies with sufficient data for a trend test showed a statistically significant exposure-response relationship (probability < one in 10 billion), i.e., increasing risk of lung cancer with increasing ETS exposure.

The study data were also combined by country, using a statistical procedure called "meta-analysis" to pool the data. Combining datasets increases the ability to detect an effect, if one is present, and provides an objective means of including all studies, both with positive and non-positive results, in the analysis. This combined analysis also showed increased risks, consistent with the analyses of the individual studies.

A number of potential modifying factors, such as diet and occupation, were also examined, and it was determined that they could not account for the observed increased risks. Furthermore, the consistency of the results across numerous independent studies from different countries argues against the existence of any one factor other than exposure to ETS as an explanation for the observed results.

In summary, the total weight of the evidence is overwhelmingly supportive of a conclusion that ETS causes lung cancer in humans, and this conclusion was unanimously endorsed by EPA's Science Advisory Board.

The population risk estimate of approximately 3,000 lung cancer deaths per year in U.S. nonsmokers is based on the pooled relative risk estimate for the 11 U.S. epidemiology studies on ETS and lung cancer, with an adjustment for other sources of ETS exposure in addition to spousal smoking. The adjustment uses biological markers of ETS exposure to assess relative ETS exposure between nonsmokers with and without spousal exposure. The estimate of 3,000 is consistent with estimates generated in an alternative analysis based on the Fontham et al. study. This NCI-funded multicenter study was the largest U.S. case-control study and is considered representative of the U.S. population. It was designed specifically to examine ETS and lung cancer and pays special attention to eliminating smoker misclassification bias. Furthermore, it is the only study which provided data on both relative risk and relative exposure.

The overall estimate of 3,000 lung cancer deaths is a composite of estimates of 1,500 for female never-smokers, 500 for male never-smokers, and 1,000 for long-term former smokers of both sexes. (These estimated 1,000 ETS-attributable lung cancer deaths in long-term former smokers are in excess of any lung cancer deaths resulting from former smoking.) To extend the analyses of female never-smokers to male never-smokers and to long-term former smokers, the estimated relative risks were converted to excess risks, and these excess risks were assumed to apply to the male never-smokers and the former smokers. This assumption may underestimate the risk in male never-smokers and long-term

former smokers, since, for example, males are exposed to greater levels of background ETS. An alternate breakdown of the estimated 3,000 lung cancer deaths attributes 800 deaths to "spousal" (or home) exposure and 2,200 deaths to other sources of exposure, such as work and public places. The EPA has relatively high confidence in these estimates, especially those for female never-smokers, since they are based on increased risks observed in humans exposed to ETS at actual environmental levels.

The epidemiology data on workplace exposure were not included in the report for several reasons. The database is much smaller than the database for females and spousal smoking, with only 10 of the 30 studies reporting data for workplace exposures. Furthermore, workplace exposures are much more variable over time, with study subjects and their coworkers typically changing jobs several times during a lifetime. In addition, the presence of other hazardous chemicals in some workplaces can make interpretation of the results more difficult. The data on female never-smokers and spousal smoking provide the largest database for the purposes of analyzing comparable data, and spousal smoking is a major source of ETS exposure that is relatively stable over time. The inference can be made that if exposure to ETS at home can cause lung cancer, exposure to comparable levels from other sources can also increase the risk. The EPA report documents exposure studies showing that ETS levels in workplaces where smoking occurs are comparable to levels in homes where smoking occurs.

Noncancer Respiratory Disorders

The weight of evidence for the noncancer respiratory disorders includes mechanistic information on tobacco smoke's effects on the lung, as well as data from over 100 epidemiological studies. Both maternal smoking during pregnancy and postnatal exposure to ETS can predispose a child to a variety of respiratory effects that can themselves have long-term consequences. Maternal smoking during pregnancy can affect the developing lung, causing permanent changes in lung structure and function, e.g. decreased lung elasticity. Postnatal exposures to ETS may similarly affect lung development, as well as increase bronchial responsiveness and enhance the process of allergic sensitization of the lung. These changes may predispose children to acute lower respiratory tract infections early in life, and to asthma, lower levels of lung function, and chronic airflow limitation later in life.

Epidemiology studies have consistently demonstrated increased risks of lower respiratory tract infections in young children whose parents smoke. In addition, epidemiology studies of children show that ETS exposure is causally associated with increased prevalence of fluid in the middle ear, symptoms of upper respiratory tract irritation (e.g., coughing and wheezing), and reductions in lung function. ETS exposure is also causally associated with additional episodes and increased severity of symptoms in children with asthma. Furthermore, the data are suggestive that ETS exposure can cause new cases of asthma in children who

have not previously displayed symptoms; however, there were too few studies to make a conclusive determination. No conclusions could be drawn about upper respiratory tract infections (i.e., colds and sore throats) or middle ear infections in children. The epidemiology studies of noncancer respiratory disorders in nonsmoking adults generally relied on spousal smoking as a surrogate for ETS exposure, and also demonstrated significant effects, including coughing, phlegm production, chest discomfort, and reduced lung function.

Because of the widespread exposure to ETS and the high incidence rates for respiratory illnesses and disorders, even small increases in risk can result in substantial numbers of cases being attributable to ETS. For example, acute lower respiratory tract infections are one of the leading causes of morbidity and mortality during infancy and childhood, and the EPA report estimates that ETS exposure is responsible for 150,000 to 300,000 cases in children up to 18 months, resulting in 7,500 to 15,000 hospitalizations, each year. Fluid in the middle ear is another common affliction in young children and is the most common reason for hospitalization of young children for an operation. As a final example of the public health impacts of ETS exposure, the EPA estimates that as many as one million asthmatic children have their condition worsened by exposure to ETS.

Other Assessments of ETS and Respiratory Disease

EPA's conclusions on the respiratory effects of passive smoking confirm and strengthen those of earlier assessments by the U.S. Surgeon General (1986), and the National Research Council of the National Academy of Sciences (1986). The World Health Organization has also concluded that ETS causes excess risk of lung cancer (1986) and other respiratory disorders (1992). The National Institute of Occupational Safety and Health (1991) concluded that occupational exposure to ETS causes increased risks of lung cancer and probably heart disease. The position of the National Cancer Institute (1993) is that ETS is a proven cause of lung cancer in nonsmoking adults and is associated with an increased risk of coronary heart disease.

New Studies on ETS and Respiratory Effects

Since the cutoff date for literature inclusion in the EPA report, several new studies have been published which provide additional evidence of respiratory effects from ETS exposure. Six of these are particularly relevant, one each on sudden infant death syndrome (SIDS) and asthma, and four on lung cancer.

In reviewing the evidence on ETS and SIDS, the EPA report concluded that there is strong evidence that infants whose mothers smoke are at an increased risk of dying from SIDS. Available studies did not allow us to differentiate whether and

to what extent this increase is related to *in utero* versus postnatal exposure to tobacco products. However, a recent study by Schoendorf and Kiely in Pediatrics found a two-fold increased risk of SIDS for infants whose mothers suspended smoking during pregnancy but resumed after giving birth, and a three-fold increased risk among infants whose mothers smoked both during and after pregnancy.

A new study on ETS and asthma by Chilmonczyk and coworkers in The New England Journal of Medicine confirmed EPA's conclusions with a finding that among children with asthma, acute exacerbations increased with ETS exposure. Asthmatic children reported to be exposed to the mother's and other persons' smoke demonstrated decreased pulmonary function and had an 80% increase in the number of acute episodes of asthma compared to children exposed only to background levels of ETS. Reported exposures, asthma exacerbation, and decreased pulmonary function also correlated with urinary cotinine measurements.

Three recent studies on ETS exposure and lung cancer in non-smoking women add to the database of the 30 studies analyzed in the EPA report. Two of these, Stockwell et al. (Journal of the National Cancer Institute) and Brownson et al. (American Journal of Public Health), are large U.S. case-control studies which find significantly increased risks among nonsmoking women in the highest category of ETS exposure, based on the amount their husbands smoked. Similar

results are reported in the very recent study of nonsmoking Chinese women by Liu et al. (American Journal of Epidemiology) who also found a statistically significant increase in risk in the most exposed group, based on husband's smoking. In addition, Stockwell et al. found significantly increased risks for high levels of household exposure as children.

Finally, an autopsy study by Trichopoulos et al. (Journal of the American Medical Association) found a significant increase in "epithelial, possibly precancerous, lesions" in the lungs of nonsmoking Greek women who were married to smokers and who had died of causes other than respiratory diseases. This finding, using a different methodology from the reports cited above, provides additional support to the weight of evidence linking passive smoking to lung cancer.

Comparison of Risk from ETS with those from other Environmental Hazards

I believe we should put the risks associated with ETS into perspective. The EPA estimates that about 20 to 30 percent of all lung cancers caused by factors other than smoking are attributable to environmental tobacco smoke. Another way of expressing this is that the increased risk of dying from lung cancer is about 1-in-1,000 from all ETS exposures outside the home. Exposure to ETS varies, but higher exposures are associated with higher risks. For example, people whose spouses smoke in the home face an average increased risk of 2-in-1,000.

Estimated risks in this range are considered high. For comparison, EPA generally sets its standards or regulations so that increased risks are below 1-in-10,000 to 1-in-1 million. In other words, the increased lung cancer risks associated with exposure to environmental tobacco smoke are at least an order of magnitude greater than the cancer risks for virtually any other chemical or agent that EPA regulates.

The additional risks on childhood respiratory health make an even more compelling case for appropriate actions to control involuntary exposures.

RESPONSES TO CRITICISMS RAISED BY THE TOBACCO INDUSTRY

CRITICISM: EPA's lung cancer conclusion depends on a "meta-analysis", a highly speculative statistical procedure.

RESPONSE: The conclusion that ETS is a human lung carcinogen, which was unanimously endorsed by the EPA's Science Advisory Board (SAB), was based on the total weight of the evidence and does not rely on the meta-analysis. The meta-analysis was only one of several analyses used to evaluate the ETS epidemiology data. All of the analyses found evidence of an association between ETS and lung cancer. Furthermore, the meta-analysis was used as an objective tool, since it provides a means of including both positive and non-positive study results into the analysis. Finally, the meta-analysis procedure was specifically approved by the SAB as appropriate for analyzing the ETS epidemiolgy database.

CRITICISM: EPA loosened its judgement criteria specifically for this risk assessment from 95% to 90% confidence intervals. Without this loosening, the results would not be statistically significant.

RESPONSE: The 90% confidence interval is consistent with the one-tailed significance test which was used in both draft reports as well as in the final report. We believe that a 90% certainty level is fully appropriate for this assessment,

given the known positive association between active smoking and lung cancer, with dose-response trends down to very low levels. Furthermore, the conclusions are not dependent on the 90% confidence interval criterion. Several of the analyses conducted demonstrate with much greater than even 95% certainty that the full set of results did not occur by chance. This methodology was also endorsed by EPA's Science Advisory Board.

CRITICISM: 80% of the epidemiology studies of ETS and lung cancer showed no increased risk.

RESPONSE: Even using the weakest exposure surrogate measure, spousal "ever" vs. "never" smoking, 24 of the 30 studies did find an increased risk, and 9 of these were statistically significant. This proportion of statistically significant positive studies is highly unlikely to occur by chance (probability $<$ 1 in 10,000). In addition, many of the studies were small and had a low statistical power to detect an effect at environmental exposure levels, especially since the study results are based on whether or not the spouse smokes, which is a crude measure of ETS exposure. A better indicator of exposure is provided by the studies that collected data on exposure level, i.e., on the amount the spouse smokes. All 17 studies with exposure level data found an increased risk in the highest exposure group; 9 of these were statistically significant, despite most having small sample size. This proportion of statistically significant studies is extremely unlikely to

occur by chance (probability < 1 in 10 million). Even more revealing, 10 out of the 14 studies with sufficient data for a trend test show statistically significant exposure-response relationships; the probability of this occurring by chance is less than one in ten billion.

CRITICISM: EPA excluded the largest U.S. case-control study, the NCI-funded study by Brownson, which showed no increased risk.

RESPONSE: EPA excluded the Brownson study (Am J Public Health, November, 1992), as well as four other recent positive studies relating to ETS and lung cancer, because they were published after the cut-off date for literature inclusion. While the overall risk is not increased in the Brownson study, the risk in the highest exposure group is statistically significantly increased. Brownson's own conclusions are stated, "Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking." Inclusion of these recent studies would, if anything, have strengthened the conclusions of the EPA report.

CRITICISM: EPA excluded data on workplace exposure, which show no excess risk. The EPA also excluded data on males.

RESPONSE: The EPA assessment focused on the data for female never-smokers and spousal smoking because spousal smoking represents the best single indicator of ETS exposure, and because these data provide, by far, the largest database for statistical analysis. The data both on males and on workplace exposures are far fewer. In addition, workplace exposures tend to be much less stable over the years, and some workplaces are sources of exposure to other various hazardous chemicals, which could make the results more difficult to interpret.

CRITICISM: Other studies show that diet can affect lung cancer risk. EPA failed to consider diet in its analysis.

RESPONSE: The EPA did consider diet and other potential modifying factors, and determined that these cannot account for the observed increased risks. Furthermore, the consistency of the results and exposure-response trends across numerous independent studies from 8 different countries argues against the existence of any one factor other than exposure to ETS as an explanation for the results.

Testimony
Hearing on the Environmental Protection Agency
Environmental Tobacco Smoke Study

House Committee on Agriculture
Subcommittee on Specialty Crops and Natural Resources
July 21, 1993

by
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Analytical Chemistry Division
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Prepared July 19, 1993

My name is Michael R. Guerin. I am head of the Organic Chemistry Section in the Analytical Chemistry Division of the Oak Ridge National Laboratory, Oak Ridge, Tennessee. I have been involved in studies of the chemistry of cigarette smoke since 1968. My group has performed research sponsored by both government agencies and tobacco industry consortia in the general areas of mainstream smoke chemistry, instrumentation for tobacco smoke inhalation toxicology, and the chemistry of environmental tobacco smoke. Our expertise in this area is the development and application of methods for the measurement of tobacco smoke constituents.

I appreciate the invitation to comment on the recent EPA report (EPA/600/6-90/006F, 12/92) on environmental tobacco smoke (ETS). The report declares ETS to be a class A ("known human") carcinogen and that 3000 lung cancer deaths per year among non-smokers in the US are due to exposure to ETS. These findings are defined as being made with medium to high certainty. The study also concludes that ETS exposure is also related to respiratory illnesses in children.

In my view, the study is commendable in its scope and detail but the conclusions are presented with a greater degree of certainty than is justified. The report identifies uncertainties in the relationships between mainstream smoke and ETS, between active and passive smoking, between urinary cotinine and dose of ETS and it details many assumptions associated with components of its risk assessment model. The study then finds a "small" risk, calculates 3000 lung cancer deaths per year by multiplying the small risk by the number of people in national subpopulations, and presents its conclusions with "medium to high certainty".

I expect that the level of certainty is bolstered by the arguments that ETS is related to mainstream smoke and that passive smoking is related to active smoking. ETS is related to mainstream smoke only in that it contains the same chemicals when first dispersed into the air. Mainstream smoke contains the chemicals at up to one million times greater concentrations, more of the chemicals are in the particle (tar) phase of mainstream smoke, and mainstream contains reactive constituents not or unlikely to be present in ETS. Adding these differences to the differences between passive smoking (normal inhalation) and active smoking (draw into the mouth, partial deep inhalation, forced exhalation) further lessens the relationship between health effects of smoking and ETS exposure. The argument that ETS can be classified as a Class A carcinogen based on its relationship to mainstream smoke is questionable.

The report also identifies uncertainties in the parameters used in the risk assessment portion of its study. It identifies the relative risk estimate for spousal exposure and the background ETS exposure adjustment as probably among the most uncertain. These are the key parameters of the assessment. Its analyses of this uncertainty provides a range for the

general population lung cancers due to ETS exposure of 400-7000. This does not appear to warrant a vote of "high certainty" for the conclusions of the study.

The relevance of the subject population (females married to smokers) to the target population (the general population) can also be questioned. Spouses of smokers are likely to be less concerned about entering and remaining in obviously smoke contaminated environments than are those not accustomed to such environments. Exposures to ETS which occur in the home differ in major ways from those occurring in the public environments. The subject is in more frequent and close contact with sidestream smoke, remains in an ETS-containing environment for a longer time, and is subject to ETS residue (unexpelled ETS constituents and material re-released from, e.g., surfaces and ashtrays).

The report describes ETS as being "ubiquitous" implying that it cannot be avoided. This is largely due to measurements of nicotine in air and of cotinine in urine. Most surveys of indoor environments find, however, that the great majority of sites sampled (of those that are not obviously contaminated - smoking lounges, bars, etc.) contain very little to undetectable quantities of nicotine. Those showing low but detectable levels of nicotine contain quantities which can be accounted for by the presence of ETS for brief periods of time or the presence of ETS in the near past.

The above observations lead me to conclude that the Study findings cannot be promulgated with "high certainty". I also note that the conclusions are not communicated with recognition of the advances that have been made in controlling exposure to ETS. The estimate of 3000 lung cancer deaths due to ETS is based on levels of exposure which were common ten years ago or more. Given the studies finding of a "small risk" associated with

ETS exposure, a treatment of the effectiveness of current restriction practices on the risk to todays' non-smokers would seem important.

Studies at our laboratory and the great majority of studies reported in the scientific literature clearly demonstrate the presence of tobacco smoke chemicals in indoor air when and after smoking occurs. The quantities of many of these chemicals are present at levels only slightly elevated over those present as a result of other sources of indoor air contaminants. Some of the chemicals are present virtually solely as the result of tobacco smoke. These include nicotine and some tobacco smoke related carcinogens. Measurements of cotinine and other smoke-related chemicals in body fluids of non-smokers clearly shows that exposure to ETS is accompanied by a body dose of at least those constituents.

My opinion of the EPA Study is that it provides compelling but not conclusive evidence of a causative relationship between lung cancer in non-smokers and exposure to ETS. The Studies conclusions are based on too many assumptions to be accepted as fact. The strength of the association is so small as to be potentially overturned by a single high-quality epidemiological study which finds contrary to those reviewed by the EPA. The weight-of-evidence, however, clearly identifies ETS as a potential health risk.

I recommend that this Study be given a formal peer-review and that the review include consideration of the most current information available. I further recommend that an exposure assessment study be carried out to determine the levels of exposure encountered by the general population of non-smokers today.

American Heart Association

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Coalition on Smoking OR Health

TESTIMONY OF ALFRED MUNZER, M.D.
On Behalf of
THE COALITION ON SMOKING OR HEALTH

to the

House Committee on Agriculture
Subcommittee on Specialty Crops and Natural Resources

RE: EPA's Risk Assessment: Respiratory Health Effects of Passive Smoking

July 21, 1993

Mr. Chairman, and members of the subcommittee, I am Dr. Alfred Munzer, President of the American Lung Association. I am also Director of Critical Care and Pulmonary Medicine at Washington Adventist Hospital in Takoma Park, MD, where I specialize in the treatment of diseases of the lung. Today I appear on behalf of the American Lung Association, the American Cancer Society and the American Heart Association, united as the Coalition on Smoking OR Health.

The Coalition on Smoking Or Health was formed in 1982 and since then has been working to educate public policy leaders about issues related to tobacco, disease prevention, and health promotion. The Coalition has been successful in such projects as banning smoking on domestic airline flights, revising warning labels on cigarette packages and advertising, and obtaining warning labels on smokeless tobacco products. In addition, the Coalition is active on the state level, and has succeeded in limiting exposure to environmental tobacco smoke indoors and limiting youth access to tobacco in several states.

Tobacco use continues to be a major public health problem in the this country. It is the leading cause of preventable death, accounting for over 487,000 deaths annually in the United States. The Coalition on Smoking Or Health believes strong steps should be taken to discourage tobacco use by all segments of our population, including youth, women, and minorities who increasingly are targeted by the tobacco industry. The Coalition also seeks to protect the nonsmoker, adult and child, from environmental tobacco smoke--the focus of today's hearing.

I am pleased to appear today to discuss the Environmental Protection Agency's risk assessment, Respiratory Health Effects of Passive Smoking. The EPA did not act in isolation nor was it the first to reach the scientific conclusions contained in the risk assessment. The scientific evidence linking environmental tobacco smoke and disease has grown dramatically during the last decade, culminating in consensus in the scientific and public health communities. I would like to provide a brief review of previous findings on environmental tobacco smoke, or passive smoking, and health effects in nonsmokers to illustrate the development of this consensus over time.

The health effects of passive smoking were first reviewed twenty years ago in the 1972 report of the Surgeon General on Smoking and Health. The report concluded that,

> "an atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals."

The 1982 Surgeon General's report again examined passive smoking, this time in the context of smoking and cancer. The Surgeon General found that,

> "although the currently available evidence is not sufficient to conclude that passive causes lung cancer in nonsmokers, the evidence does raise concern about a possible serious public health problem."

In November 1986, the National Academy of Sciences issued a report, Environmental Tobacco Smoke: Measuring Exposure and Assessing Health Effects. The report concluded that ETS is associated with an approximately 30% increased risk for lung cancer in nonsmokers and that ETS has specific severe effects in respiratory health of infants and young children.

In December of the same year, the Surgeon General released a report devoted entirely to the health effects of passive smoking. The Surgeon General concluded that passive smoking is a cause of lung cancer in healthy nonsmokers. In addition, the report concluded that children whose parents smoke have an increased frequency of respiratory infections and respiratory symptoms compared with children whose parents do not smoke. The National Academy of Sciences also issued a report in 1986 that offered similar conclusions.

A third report in 1986 by the prestigious International Agency for Research on Cancer concluded that,

> "Knowledge of the nature of sidestream and mainstream smoke, of materials absorbed during 'passive smoking', and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens leads to the conclusion that passive smoking gives rise to some risk of cancer."

These reports were developed and edited by different procedures strengthening the validity of the common conclusions.

Finally, in 1991, the National Institute for Occupational Safety and Health published its Current Intelligence Bulletin, no. 54, "Environmental Tobacco Smoke in the Workplace". NIOSH concluded that ETS is a potential occupational carcinogen--the most significant category for human carcinogens used by the agency.

The Environmental Protection Agency's risk assessment not only supported these earlier findings with regard to the risks of lung cancer, it also augmented previous reports with an

exhaustive review of the health effects of environmental tobacco smoke on children. Although the tobacco industry has repeatedly tried to refute the findings of this risk assessment as they pertain to the lung cancer risks for adults, the results concerning respiratory disease in children have not received such attention. I would like, for the record, to review briefly the findings regarding the risks for children when they are exposed to environmental tobacco smoke:

- 8,000 to 26,000 cases of childhood asthma per year are attributable to environmental tobacco smoke;
- 200,000 to 1 million children already diagnosed with asthma have a significant worsening of their symptoms due to environmental tobacco smoke;
- 150,000 to 300,000 cases annually of lower respiratory tract illness in young children under 18 months are attributable to environmental tobacco smoke;
- 7,500 to 15,000 hospitalizations in these younger children result from exposure to environmental tobacco smoke; 15,000 hospitalizations for lower respiratory tract illness would equate to between $45 million and $68 million annually, given the average cost per patient with such a diagnosis.

Long before the January 7, 1993 release of the Environmental Protection Agency's risk assessment and its finding that environmental tobacco smoke is a Group A, known human carcinogen the scientific, medical and public health communities reached an overall consensus regarding the link between ETS and serious disease. In fact, given the mounting evidence in recent years, the fundamental question that follows from this consensus is,

"Why did it take the Agency so long to initiate and complete its risk assessment?"

Today's hearing focuses on a false tobacco industry-concocted controversy about the risks of exposure to environmental tobacco smoke. The controversy has been generated by an industry that still questions whether direct active smoking kills, even in light of the more than 50,000 studies that demonstrate this fact. The tobacco industry's campaign of controversy regarding the EPA risk assessment parallels the attacks it has leveled at the Surgeon General's Reports on Smoking and Health since the initial report was published in 1964. Given the tobacco industry's continuing campaign of deception and denial, it is instructive to quote from the preface to the 1979 Surgeon General's Report on Smoking and Health. Then Secretary of Health, Education and Welfare, Joseph A. Califano, Jr. wrote,

> "In truth, the attack upon the scientific and medical evidence about smoking is little more than an attack upon the science itself: an attack upon the epidemiological, clinical, and experimental research disciplines upon which these conclusions are based. Like every attack upon science by vested interests, from Aristotle's day to Galileo's to our own, these attacks collapse of their own weight."

The tobacco industry would have the debate continue even longer, arguing with the methodological approach taken by the Environmental Protection Agency and, in general, portraying the report as "poor" science. From my years as a volunteer with the American Lung Association, I am aware of the long liaison between the Lung Association and the EPA and the high regard with which the Agency's research program on air pollution is held. None of us should forget EPA's achievements in controlling in air pollution from a variety of

sectors, including emissions from cars and trucks, from oil production, from petrochemicals, from chemical manufacturing indeed from all industrial and manufacturing sectors.

The tobacco industry has constructed its campaign of controversy and themes of poor science with questions about statistical significance, meta-analysis, confidence intervals, use of the Agency's cancer guidelines, etc. The industry, in making its criticisms, implies capricious and irresponsible behavior on the part of the Agency's scientific and administrative staff. However, it must be noted that all decisions regarding the development of the risk assessment were made in conjunction with and agreed upon by an independent body of scientists, the Agency's Scientific Advisory Board, Indoor Air Quality and Total Human Exposure Committee. In fact, this committee was highly criticized by members of Congress and the scientific community early in the developmental phase of the risk assessment as biased toward the tobacco industry.

Dr. Dockery will discuss some of the methodological issues raised about the report. I therefore, will conclude with a discussion of the misinterpretation of results and findings of several studies by the tobacco industry to further its claims of "poor" science.

The Tobacco Institute, in materials distributed at the time of the release of the final risk assessment, argues that recently published studies on environmental tobacco smoke, including one of the largest studies to date and funded by the National Cancer Institute, reported no statistical significant increase in risk. The Tobacco Institute also asserts that the

Agency chose not to include such studies in the risk assessment because their conclusions would have changed dramatically. Foremost among the more recent studies cited by the industry is the Brownson study, "Passive Smoking and Lung Cancer in Nonsmoking Women". Am J Public Health, 82:1525-30, 1992. In reality, the Environmental Protection Agency excluded the Brownson study as well as three other positive studies regarding environmental tobacco smoke and lung cancer because they were published after the cut-off date for literature inclusion. The Agency had been under pressure from Congress and the medical community to complete the risk assessment. Nonetheless, the Brownson study provides no support for the tobacco industry argument. On the contrary, Brownson found risk in the highest exposure group is statistically significantly increased. Brownson's own conclusions are stated,

> "Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking. Comprehensive actions to limit smoking in public places and worksites are well-advised."

Similarly, the Stockwell study, "Environmental Tobacco Smoke and Lung Cancer in Nonsmoking Women". J Natl Cancer Inst, 84:1417-22, 1992, was also not included in the EPA risk assessment. The tobacco industry claims this to be a negative study and therefore left out purposefully. However, the authors state,

> "In conclusion, the results described here suggest that long term exposure to environmental tobacco smoke increases the risk of lung cancer in women who are nonsmokers. Risks appeared most elevated for non-adenocarcinoma lung cancers. High levels of exposure during youth and adulthood may each play a role in increasing lung cancer risk."

Inclusion of such studies would, if anything, have strengthened the conclusions of the risk assessment.

Despite the tobacco industry campaign of attempting to create a false controversy, more and more Americans understand that environmental tobacco smoke is harmful. That understanding is revealed in public opinion surveys conducted by the Gallup Organization for the American Lung Association. In the most recent survey, conducted in 1992, 9 in 10 adults were aware that environmental tobacco smoke is harmful to infants and young children, pregnant women, and older healthy adults. Women were more likely than men to believe that environmental tobacco smoke is harmful to all of these groups. Nonsmokers also were more likely than smokers to strongly agree about the harmful effects of environmental tobacco smoke. An important finding was than even 8 in 10 smokers know that environmental tobacco smoke is bad for the people around them.

In summary, given the accepted consensus in the medical, scientific, and public health communities about the risks of environmental tobacco smoke and the growing public awareness of these risks, change is inevitable for those who grow tobacco. Everyone would be better served if we focused on how to best manage that change rather than to continue to deny the health hazards of tobacco use. Mr. Chairman, you have long been a champion of the family farmer. We want to offer our support for reasonable measures designed to assist the family tobacco farmer during the ongoing transition to non-tobacco crops. The Coalition has offered to participate in such efforts before and, has done so sincerely.

Thank you.

Coalition on Smoking OR Health

TESTIMONY OF DOUGLAS W. DOCKERY

On Behalf of

THE COALITION ON SMOKING OR HEALTH

to the

House Committee on Agriculture
Subcommittee on Specialty Crops and Natural Resources

RE: EPA's Risk Assessment: Respiratory Health Effects of Passive Smoking

July 21, 1993

HARVARD SCHOOL OF PUBLIC HEALTH
Department of Environmental Health
Environmental Epidemiology Program

Procedural and scientific issues relating to the environmental tobacco smoke report released by the EPA on January 7, 1993. Hearing of the Subcommittee on Specialty Crops and Natural Resources. July 21, 1993

Prepared testimony by Douglas W. Dockery, Associate Professor of Environmental Epidemiology

Thank you for the invitation to testify on the scientific issues surrounding the environmental tobacco smoke report[1] released by the EPA on January 7, 1993. In the invitation letter, Mr. Rose suggested that the Subcommittee would consider issues relating to the risk assessment procedures, including: application of the Agency's Carcinogen Classification Guidelines to data on ETS; EPA's evaluation of the ETS data, including its use of the meta-analysis technique, its selection of particular epidemiologic studies to include in its analysis, and the statistical methodology employed; and other EPA risk assessment projects, including how the relevant data bases compare with those for ETS. Let me discuss each of these issues separately.

Criteria for Classifying ETS as a Carcinogen

Tobacco smoke is a known cause of lung cancer. The carcinogenicity of tobacco smoke has been demonstrated by all methods used to assess risk -- that is, in animal bioassay studies, genotoxicity studies, and epidemiologic studies. Moreover, tobacco smoke is a strong carcinogen. Epidemiologic studies have shown that active-smokers develop lung cancer at a rate at least ten times that of never-smokers. Epidemiologic studies have shown that the risk of lung cancer associated with tobacco smoke increases with exposure, measured either by number of cigarettes smoked per day, or years of cigarette smoking. There is no evidence from these studies of active smokers that there the smallest exposures to active smoking are free of risk. It follows immediately that exposures to low concentrations of tobacco smoke should be associated with increased risk of lung cancer. **The evidence that tobacco smoke is such a strong cause of lung cancer, without any other consideration, is sufficient to define environmental tobacco smoke as a lung-cancer hazard.**

There is also substantial evidence showing that nonsmokers are passively exposed to tobacco smoke at nontrivial levels. That nonsmokers are breathing environmental tobacco smoke, and are therefore at risk of developing the same diseases as active-smokers, is a fact so clear that it should require no further discussion. Nevertheless, a considerable mass of data has been developed estimating environmental exposures to tobacco smoke, direct measurements of ambient indoor concentrations of tobacco smoke, and direct measures of dose based on biologic tissue samples. **The evidence that large numbers of people in the general population are exposed**

to this carcinogen is sufficient to define environmental tobacco smoke as a lung-cancer hazard.

Given that tobacco smoke is associated with increased incidence of lung cancer even to the lowest exposures among active-smokers, and that there is widespread environmental exposure to tobacco smoke among nonsmokers, increased incidence of lung cancer should be expected among never-smokers chronically exposed to environmental tobacco smoke. Indeed, increased incidence of lung cancer has been consistently observed in studies of never-smokers exposed to environmental tobacco smoke. Moreover, we also should expect to observe increased incidence of other cancers associated with active tobacco smoking among never-smokers environmentally exposed to tobacco smoke. **Evidence from epidemiologic studies that never-smoking women with smoking spouses have increased risk of lung cancer only confirms what was apparent from the carcinogenicity of tobacco smoke itself.**

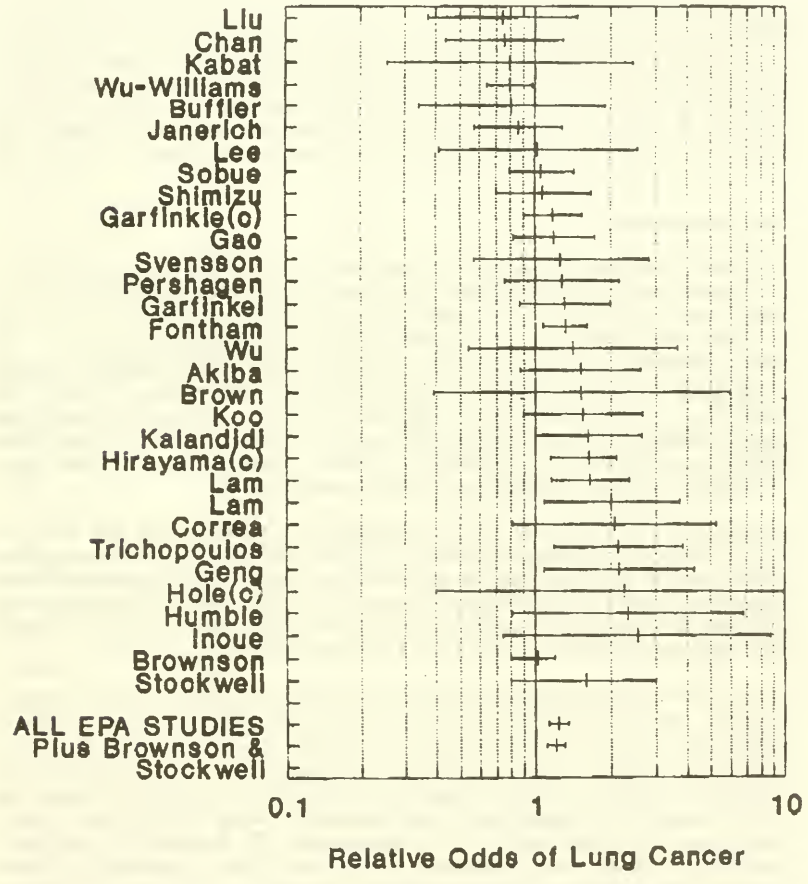
Use of Meta-Analysis

Given the compelling evidence cited above, the hypothesis to be tested is not that tobacco smoke has no statistically signficant association with lung cancer in epidemiologic studies. Rather, the hypothesis to be tested is that environmental tobacco smoke does not increase lung cancer risk. Of the 30 studies reviewed by the EPA[1] only one study[2] was not consistent with an increased lung-cancer risk associated with spouse smoking. The consistency of these results across so many independent studies showing a positive association between lung cancer and spousal smoking is a very strong statement of the robustness of those findings. In epidemiologic studies of effects of environmental hazards, such consistency and robustness is a much more important indicator of causality than statistical significance.

The attached figure presents my summary of the available epidemiology data showing the association of lung cancer in non-smoking women with the cigarette smoking of their husbands. Results from the 30 studies considered by the EPA plus two studies which appeared subsequent to the writing of the EPA report, are presented. For each study, the estimated relative odds of lung cancer associated with husband's cigarette smoking is presented along with the 95% Confidence Inerval for that estimate. A relative odds greater than one (that is, on the righthand side of the plot) indicates that lung cancer in these non-smoking women is positively associated with their husbands' smoking. It is clear from this plot that almost all of these studies have found such a positive association.

Critics have suggested that these associations may be the result of bias or counfounding in the data -- that is, that the observed associations are due to some characteristic other than spouse smoking which is related to <u>both</u> lung cancer and spouse smoking. While each study has its weakness, and bias and confounding must be considered in any study, it is my interpretation of these studies that bias and confounding have generally acted to underestimate the true association between lung cancer and environmental tobacco smoke exposure. Other design issues -- such as the fact that spouse smoking is only a crude measure of environmental tobacco smoke exposure in the home, at work, and in other settings -- will also produce underestimates of the true association.

EPIDEMIOLOGIC STUDIES OF HUSBAND'S SMOKING & LUNG CANCER



Critics have also suggested that the use of meta-analysis techniques, as in the EPA Report, are inappropriate for epidemiologic data. In this I strongly disagree. Meta-analysis is a well-developed technique for contrasting and combining results from different studies. Its concepts and methods are actually a simple extension of statistical analysis already used in epidemiology. These methods are commonly used in public health research, particularly in the evaluation of clinical trials[3]. Meta-analysis has been applied in epidemiologic research for many decades[4] and has recently been the subject of two scholarly reviews[5,6]. The use of these methods by the EPA is not only appropriate but is a significant advance in evaluating the scientific literature.

Meta-analysis is significant because it provides an objective method for combining data and for evaluating effects estimates from different studies. Moreover, it provides a method for contrasting various studies in the literature and for evaluating the effects of bias, confounding, and other issues of importance in epidemiological studies. For these reasons, I think that the EPA analysis, following similar meta-analyses of ETS and lung cancer by the National Academy of Sciences[7] and the U. S. Surgeon General[8], has been most responsible in applying this technique to an environmental agent. I strongly support the use of meta-analysis in rule-making.

Selection of Studies

As far as I can tell, the EPA report included all studies available at the time of writing. With the continual publication of new studies showing the adverse effects of environmental tobacco smoke, there comes some point, largely determined by forces outside the control of the reviewers, when the writing stops. The EPA Report was published in December 1992. The study by Brownson et al.[9] appeared in the November-1992 issue of the American Journal of Public Health (which means it arrived in my office in late November or early December). The Stockwell et al paper[10] appeared in the September-1992 issue of the Journal of the National Cancer Institute. Given these publication dates, one can hardly suggest that these papers were ignored because they may have "affected EPA's results." Moreover, inclusion of these papers would not have affected the meta-analysis (to be discussed later).

Attached is a copy of my own simple meta-analysis of the original EPA data, taking the weighted mean of the studies as presented in Table 5-5 of the EPA report. The combined estimate over all the studies based on the crude data presented gives me an overall effect estimate of 1.24 (with a 95% confidence internal of 1.13 - 1.35). Including the Brownson[9] and the Stockwell[10] studies in that analysis (as shown in the attached table) only minimally changes the overall effect estimate to 1.21 (with a 95% confidence interval of 1.11 - 1.31).

If a decision were to be based on a single study, I consider the Fontham et al[11] study to be the best study, and certainly the statistically most powerful study, conducted so far. Its power is indicated by the weights given to this study in my attached meta-analysis. It has the strength of being a prospective study -- looking at 420 incident primary lung cancers that are pathologically confirmed -- with very good exposure estimates and very good definition of the health outcomes. The Brownson[9] study is also a large study, having 432 lifetime non-smokers, and also has a high weight given to it in the meta-analysis. The weakness of this study is the relatively poor exposure data, as compared to the Fontham study. Nevertheless, a positive association was found between spouse smoking and lung cancer which increased with years of

Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects.

Summary of Epidemiologic Studies of Risk Based on Exposure Assessed by Spouse Smoking Habits When Available, or Smoking by Household Cohabitants. Data from Table 5-5 (US EPA,1992).

Authors	Year	OR	90% CI Lower	90% CI Upper	Var (lnOR)	Weights	ln(OR)* Weight
CASE-CONTROL STUDIES							
Akiba et al.	1986	1.52	0.96	2.41	0.078	12.78	5.36
Brownson et al	1987	1.52	0.49	4.79	0.480	2.08	0.87
Buffler et al.	1984	0.81	0.39	1.66	0.194	5.16	-1.09
Chan and Fung	1982	0.76	0.48	1.19	0.076	13.13	-3.78
Correa et al.	1983	2.07	0.94	4.52	0.228	4.39	3.19
Fontham et al	1991	1.32	1.08	1.61	0.015	67.90	18.85
Gao et al	1987	1.19	0.87	1.63	0.036	27.46	4.78
Garfinkel et al.	1985	1.31	0.93	1.85	0.044	22.88	6.18
Geng et al	1988	2.16	1.21	3.84	0.123	8.12	6.25
Humble et al.	1987	2.34	0.96	5.69	0.293	3.42	2.91
Inoue & Hirayama	1988	2.55	0.9	7.2	0.399	2.50	2.34
Janerich et al.	1990	0.86	0.57	1.29	0.062	16.23	-2.46
Kabat and Wynder	1984	0.79	0.30	2.04	0.339	2.96	-0.89
Kalandidi et al. *	1991	1.62	0.99	2.65	0.063	15.85	7.65
Koo et al.	1987	1.55	0.98	2.44	0.077	13.01	5.70
Lam	1985	2.51	1.49	4.23	0.101	9.94	9.15
Lam et al.	1987	1.65	1.22	2.22	0.033	30.20	15.12
Lee et al.	1986	1.03	0.48	2.20	0.214	4.67	0.14
Liu et al.	1991	0.74	0.37	1.48	0.178	5.63	-1.70
Pershagen et al. *	1987	1.28	0.82	1.98	0.051	19.77	4.88
Shimizu et al.	1988	1.08	0.7	1.68	0.071	14.12	1.09
Sobue	1990	1.06	0.79	1.44	0.033	30.03	1.75
Svensson et al.	1989	1.26	0.65	2.48	0.166	6.04	1.40
Trichopoulos et al.	1983	2.08	1.31	3.29	0.078	12.76	9.35
Wu et al. *	1985	1.41	0.83	3.15	0.169	5.93	2.04
Wu-Williams, Samet	1990	0.79	0.64	0.98	0.017	59.62	-14.05
Brownson et al *	1992	1.03	0.80	1.20	0.011	93.47	2.76
Stockwell et al. *	1992	1.60	0.80	3.00	0.114	8.80	4.13
COHORT STUDIES							
Butler *	1988	2.02	0.48	8.56	0.540	1.85	1.30
Garfinkel *	1981	1.17	0.85	1.61	0.027	37.66	5.91
Hirayama	1984	1.38	1.03	1.87	0.033	30.43	9.80
Hole et al. *	1989	2.27	0.4	12.7	0.778	1.29	1.05

	ORmh	95% CI Lower	95% CI Upper	Var (lnOR)	Weights	
Overall for Case-Control Studies	1.23	1.11	1.35	0.205	416.57	85.22
With Brownson and Stockwell Studies	1.19	1.10	1.30	0.178	518.84	92.12
Overall for Cohort Studies	1.29	1.02	1.63	0.254	71.23	18.07
Overall for Studies in EPA Report	1.24	1.13	1.35	0.212	487.80	103.29
With Brownson and Stockwell Studies	1.21	1.11	1.31	0.187	590.07	110.19

* 95% Confidence Intervals reported

exposure. The authors conclude: "Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking." This certainly is consistent with all the evidence that has been presented in the other studies.

Statistical Methodology

The tobacco interests have questioned the use of 90% Confidence Intervals in the meta-analysis. The Confidence Interval reflects only one of several elements that must be considered in the evaluation of epidemiologic studies: the Confidence Interval is a quantitative measure of the statistical or random error in the data and reflects, therefore, only the influence of chance in these data. It is inappropriate to define an adverse health effect by a statistical significance or a Confidence Interval; therefore, whether that definition is based on a 90% Confidence Interval or a 95% Confidence Interval is irrelevant.

Use of a 90% (rather than 95%) Confidence Interval in this case corresponds to use of a one-tailed (rather than two-tailed) test of statistical significance at the $p=0.05$ level. In the case of a known carcinogenic agent, such as tobacco smoke, it is entirely appropriate to use a one-tailed or one-sided test of significance for an adverse effect of tobacco smoke. We would not expect tobacco smoke to be a protective agent against cancer and therefore the use of a 5% one-tailed test, or equivalently a 90% Confidence Interval, is justified.

Other Risk Assessment

The tobacco interests have compared EPA's risk assessment of environmental tobacco smoke (ETS) with risk assessments of electromagnetic radiation (EMF) and of chlorinated water. First, an important difference betwwen ETS and these other environmental exposures is that there is little or no supporting evidence for the EMF hypothesis available in the literature at the moment. The meta-analysis is only one component of a multi-factorial evaluation that has to be undertaken in classifying an agent as a carcinogen. While evidence for a positive association may be found for EMF, there is a lack of evidence for strong occupational effect or evidence of other effects at high-EMF exposures as is shown for direct tobacco smoke. Secondly, there is a lack of the strong toxicologic basis that has been developed for tobacco smoke.

Tobacco smoke has been shown to be a carcinogen in laboratory experiments; tobacco smoke has been shown to be a carcinogen in studies of humans actively smoking themselves, and, in multiple studies, environmental tobacco smoke has been shown to be an environmental carcinogen. There is not the same body of evidence for EMF or chlorinated water suggesting that there are effects demonstrated in laboratory experiments or at very high exposures and, until such a body of evidence is developed, it would be inappropriate to move forward with a similar finding for those particular agents.

In my opinion, the epidemiologic evidence for an association between lung cancer and environmental tobacco smoke is compelling. The EPA Report is a comprehensive, rigorous, balanced, and scholarly summation of the current state of the science which supports such a finding. While epidemiologic studies alone cannot demonstrate causality, the universal finding

of the carcinogenicity of tobacco smoke in animal and genotoxicity studies corroborates the epidemiology. There is no doubt that tobacco smoke is an environmental carcinogen.

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(Attachment follows:)

Addendum to testimony regarding
EPA REPORT ON ENVIRONMENTAL TOBACCO SMOKE

SUBCOMMITTEE ON SPECIALTY CROPS AND NATURAL RESOURCES
Hearing of July 21, 1993

DR. DOUGLAS W. DOCKERY
Associate Professor of Environmental Epidemiology
Harvard School of Public Health

In his testimony, Professor Alvin Feinstein referred to standards for determining causation of environmental associations with disease proposed by Austin Bradford Hill in 1965. I agree with Professor Feinstein that such standards should be applied in the case of Environmental Tobacco Smoke. In fact, my testimony before the EPA Science Advisory Board committee reviewing the EPA report was largely a discussion of the Bradford Hill Criteria. I have attached a copy of the material I used for that presentation, which consisted of direct quotes from Bradford Hill's article entitled "The Environment and Disease: Association or Causation?" I have included a summary of my oral comments regarding environmental tobacco smoke in italics.

AUSTIN BRADFORD HILL

The Environment and Disease: Association or Causation?

Proceedings of the Royal Society of Medicine 1965; 58:295-300.

1) **STRENGTH**

First upon my list I would put the strength of the association.

...prospective inquiries into smoking have shown that the death rate from cancer of the lung in cigarette smokers is nine to ten times the rate in non-smokers and the rate in heavy cigarette smokers is twenty to thirty times as great.

In thus putting emphasis upon the strength of an association, we must nevertheless look at the obverse of the coin. We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight.

Comments Regarding Environmental Tobacco Smoke: In the case of environmental tobacco smoke, there is clear evidence that heavy exposures lead to a very strong association, as reported here by Hill for heavy smokers. The weak associations reported with spouse smoking should not be used to "dismiss a cause-and-effect hypothesis".

2) **CONSISTENCY**

Has it been repeatedly observed by different persons, in different places, circumstances and times?

...there will be occasions when repetition is absent or impossible and yet we should not hesitate to draw conclusions.

Comments Regarding Environmental Tobacco Smoke: The epidemiologic evidence is consistently shows increased lung cancer associated with environmental tobacco smoke exposures as reported "by different persons, in different places, circumstances and times".

3) **SPECIFICITY**

...specificity of the association, the third characteristic which invariably

we must consider.

...if specificity exists, we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence.

Comments Regarding Environmental Tobacco Smoke: The associations with environmental tobacco smoke are specifically associated with lung cancer. Recent studies suggest the association may be strongest with a specific cell type - adenocarcinoma.

4) **TEMPORALITY**

...temporal relationship of the association - which is the cart and which is the horse?

Comments Regarding Environmental Tobacco Smoke: Many studies of environmental tobacco smoke exposure show the strongest associations among women with the longest histories of exposures. Other studies suggest associations with environmental tobacco smoke exposures in childhood. Clearly environmental tobacco smoke exposure is preceding lung cancer.

5) **BIOLOGICAL GRADIENT**

...if the association is one that can reveal a biological gradient, or dose-response curve, then we should look most carefully for such evidence.

Comments Regarding Environmental Tobacco Smoke: A dose - response gradient of increased risk of lung cancer with number of years of environmental tobacco smoke exposures, or number of cigarettes smoked per day by the husband has been consistently reported in epidemiologic studies.

6) **PLAUSIBILITY**

It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the

day.

Comments Regarding Environmental Tobacco Smoke: Given that tobacco smoke causes lung cancer in active smokers, it is entirely plausible that small exposures from environmental tobacco smoke should cause small increased incidence of lung cancer in nonsmokers.

7) **COHERENCE**

...cause-and-effect interpretation of our data should not seriously conflict with the generally-known facts of the natural history and biology of the disease.

Comments Regarding Environmental Tobacco Smoke: The evidence for environmental tobacco smoke being associated with increased lung cancer is coherent with the known " natural history and biology of the disease".

8) **EXPERIMENT**

Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association, some preventive action is taken.

Comments Regarding Environmental Tobacco Smoke: It would clearly be unethical to experimental expose subjects to environmental tobacco smoke. However, the potential for reduced lung cancer in nonsmokers twenty to thirty years from now should be evaluated given the reductions in exposure expected from the EPA designation of environmental tobacco smoke as a Class A carcinogen.

9) **ANALOGY**

In some circumstances it would be fair to judge by analogy.

Comments Regarding Environmental Tobacco Smoke: The analogy of lung cancer risks between active tobacco smoking and environmental tobacco smoking is sufficient to designate environmental tobacco smoke as a carcinogen.

TESTS OF SIGNIFICANCE

No formal tests of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create and they will instruct us in the likely magnitude of those effect. Beyond that, they contribute nothing to the 'proof' of our hypothesis.

Comments Regarding Environmental Tobacco Smoke: Tests of significance, as Hill points out here, do not contribute to the proof of causation. The arguments mounted regarding statistical issues of one-sided verses two-sided tests, or 90% versus 95% confidence intervals, are only intended to obscure the issues and suggest there is controversy when indeed there is none.

CONCLUSIONS

All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the actions that it appears to demand at a given time.

Comments Regarding Environmental Tobacco Smoke: The association of environmental tobacco with lung cancer meets each of the criteria proposed by Hill for establishing causation. While it can be argued that the data are incomplete, there is clear, consistent, and compelling data available which mandates action. A call for new studies will postpone actions which are demanded by the existing data. The EPA has objectively reviewed the available data and has drawn the only reasonable conclusion. Environmental tobacco smoke meets the tests for causation of lung cancer in human studies.

COMMITTEE ON AGRICULTURE
SUBCOMMITTEE ON SPECIALTY CROPS AND NATURAL RESOURCES
U.S. HOUSE OF REPRESENTATIVES

A CRITICAL APPRAISAL OF THE REPORT ON ENVIRONMENTAL TOBACCO SMOKE ISSUED BY THE U.S. ENVIRONMENTAL PROTECTION AGENCY ON JANUARY 7, 1993

Statement of
Dr. Gio Batta Gori
The Health Policy Center
Bethesda, Maryland

JUNE 1993

SUMMARY

- EPA HAS A HISTORY OF BENDING SCIENCE TO SUIT POLICY
- EVEN BEFORE ITS OWN STUDY OF THE EVIDENCE EPA HAD DECIDED TO STRIKE AGAINST ETS
- EXTREME DILUTION OF ETS PREVENTS OBJECTIVE IDENTIFICATION AND RESULTS IN NOMINAL EXPOSURES
- EPIDEMIOLOGIC STUDIES OF ETS EXPOSURE ARE INCONSISTENT, UNINTERPRETABLE, AND MOST ARE NOT STATISTICALLY SIGNIFICANT
- EPA HAS SYSTEMATICALLY SELECTED ONLY DATA THAT SUPPORT ITS CONCLUSIONS
- EPA FAILED TO STATE THAT ITS RANGE OF RISK ESTIMATES SHOULD INCLUDE ZERO, OR NO RISK AT ALL
- EPA'S ARBITRARY PROCEDURES REPRESENT A THREAT TO FREEDOM IN A DEMOCRATIC SOCIETY
- REFERENCES

Mister Chairman, Members of the Committee:

My name is Gio Batta Gori. I am a toxicologist with training in epidemiology and broad interests in smoking and health, cancer causation and risk assessment. I am President of the International Society of Regulatory Toxicology and Pharmacology, and a Fellow of the Academy of Toxicological Sciences. In the 1960's and 1970's, I was Deputy Director for Cancer Cause and Prevention at the National Cancer Institute, where I received the Public Health Superior Service Award in 1977 for activities as Director of the Smoking and Health Program. My full curriculum vitae is appended to the written statement submitted at this hearing.

The Tobacco Institute has asked me to explain my concerns as a scientist about the report on environmental tobacco smoke (ETS) released by the Environmental Protection Agency (EPA) on January 7, 1993 (1). My views, nevertheless, are my own and are not necessarily those of The Tobacco Institute.

EPA HAS A HISTORY OF BENDING SCIENCE TO SUIT POLICY

The EPA report on ETS is a glaring example of the misuse of science in support of preconceived policy aims. It is not unique, but it is possibly the most egregious example in a well-documented tradition of scientific abuse at EPA.

In 1991, an independent blue ribbon panel was convened by then-Administrator Reilly to investigate concerns that had been voiced about the quality of science at the Agency. The panel concluded that the Agency does not have a coherent science agenda and suffers from poor scientific credibility because it has not secured adequate external support from the scientific community at large (2). More to the point, the panel concluded that EPA's science often seems to have been adjusted to endorse policy, an especially relevant remark when considering the Agency's report on ETS.

EPA's own research director, Dr. Erich Bretthauer, recently lamented that the agency too often pays more attention to media headlines than to scientific evidence. And at the press briefing following the release of the ETS report, Dr. Bretthauer acknowledged that the EPA's $26 billion cost estimate for the Clean Air Act implementation may prevent fewer than 100 lung cancer cases a year, and possibly none at all. This is a typical example of overregulation by EPA without solid scientific support.

EVEN BEFORE ITS OWN STUDY OF THE EVIDENCE EPA HAD DECIDED TO STRIKE AGAINST ETS

As far as ETS is concerned, the Agency's staff disclosed its predisposition against ETS long before the report was even drafted. In 1989 EPA disseminated a so-called "fact sheet" asserting that ETS is a known cause of lung cancer and other diseases. The same claim was made in a 1990 draft policy guide aimed at banning smoking in workplaces. In its final report itself, the Agency had no hesitation in writing that its analysis was based "on the a priori hypothesis . . . that a positive association exists between exposure to ETS and lung cancer." (1, p. 5-2).

The agency and its Science Advisory Board conceded that ETS could be classified as a Group A carcinogen only if the Agency's guidelines for carcinogen assessment -- guidelines that reflected established scientific principles -- were disregarded. In a telling statement, the SAB panel reviewing the ETS risk assessment declared: "If the guidelines for Carcinogen Risk Assessment can be used to cast doubt on a finding that inhalation of tobacco smoke by humans causes an increased risk of lung cancer, the situation suggests a need to revise the guidelines." (3, p. 28).

EXTREME DILUTION OF ETS PREVENTS OBJECTIVE IDENTIFICATION AND RESULTS IN NOMINAL EXPOSURES

A first requirement of EPA's guidelines -- and also an intuitively correct one -- is that the substance considered be positively identified. However, what substance is EPA dealing with? The report itself is forced mostly to speculate about ETS components. Only about twenty have been identified with some confidence as being found in ETS, although most could come from other sources as well. Other components cannot be measured because of extreme dilution. EPA sought to evade the problem by arbitrarily declaring that ETS is equivalent to the smoke that smokers inhale.

Never mind that the agency's Science Advisory Board admonished EPA's staff that the alleged equivalency of ETS and cigarette smoke could not be scientifically sustained. Never mind that the EPA report itself discounts this similarity in its fine print. Never mind that the EPA report itself agrees that exposures to ETS components are tens of thousands to a million fold less than for cigarette smokers, and far below the levels permitted for such components in workplaces by the Occupational Safety and Health Administration (1,4).

In fact, if EPA were correct with regard to ETS it would be necessary, for the sake of consistency, to designate as human carcinogens mixtures such as vehicle exhausts, the wood and gas fires in homes, grill and barbecue fumes and others, simply because they bear similarities to coke oven emissions, which EPA already classifies as known human carcinogens.

EPIDEMIOLOGIC STUDIES OF ETS EXPOSURE ARE INCONSISTENT, UNINTERPRETABLE, AND MOST ARE NOT STATISTICALLY SIGNIFICANT

In truth, this contrived identification of ETS with mainstream cigarette smoke was needed to bolster the weak and inconclusive results of ETS epidemiologic studies. Of 30 such studies from all over the world, only six reported statistically significant associations between marriage to a smoker and lung cancer risk, and some actually reported decreased risks. The EPA based its risk assessment on 11 US studies, none of which was statistically significant overall.

To claim significance, however, EPA resorted to what the Agency staff acknowledged was "fancy statistical footwork." The gambit involved doubling the statistical "confidence interval" from the standard ± 5% point margin usually employed -- even in the first draft of the EPA report -- to a ± 10% point margin. Naturally, as if by magic the overall results became statistically significant. Yet, what any self-respecting scientist would perceive here is not confidence intervals, but rather a confidence game.

Indeed, by adopting a ±10% instead of the ±5% standard the EPA report aims to give the data an artificial impression of stability and certainty. By this gambit the data are not changed, but their intrinsic uncertainty is fictitiously reduced. Experts may see through this machination, but also understand that its only possible purpose is to pull some wool over less sophisticated eyes.

In epidemiology the 5% standard is universally prescribed as a minimum requirement. Published epidemiologic studies -- virtually without exception -- adhere to this standard. This is especially important for epidemiologic studies of potential low level risks for lung cancer, which are notoriously difficult to conduct and interpret. For instance, there is firm evidence that differences in diet, physical activity, disease experience, socioeconomic status, occupation, and other variables are associated with lung cancer risk differentials independently of ETS exposure (4). Largely ignored by the Agency, these confounders have

been shown fully capable of accounting for the small reported association between marriage to a smoker and increased risk of lung cancer. In reality, one cannot look at ETS alone, as the agency in effect has done.

A major justification advanced is that by now several studies have arrived at similar conclusions. However, this is true only if one eliminates all the contrary data and ignores that most studies suffer from the same defects and shortcomings. Illusory attempts have been made to increase the significance of these studies by combining their data in what is known as a meta-analysis exercise. Yet, it is intuitively difficult to improve the overall quality of conclusions by combining individual studies that are intrinsically flawed. Rotten apples could hardly make good applesauce.

EPA HAS SYSTEMATICALLY SELECTED ONLY DATA THAT SUPPORT ITS CONCLUSIONS

There is more. Two months before the EPA risk assessment was released, two new epidemiologic studies addressing ETS and the risk of lung cancer were published in the scientific literature (5,6). One of these, funded in part by the National Cancer Institute, is the largest case-control study published to date in the U.S. When the data from these two studies are added to EPA's analysis, the result is not statistically significant based on a standard margin of error or even on EPA's less rigorous standard. Yet EPA refused to consider these latest and clearly relevant data. It also ignored that 12 out of 14 epidemiologic studies of ETS in workplaces failed to detect any significant elevation of lung cancer risk.

To confirm EPA's unjustified conclusion with respect to ETS, consider only that in the case of electromagnetic fields the agency dismissed the epidemiologic evidence, even though 25 of some 40 available studies were statistically significant and many reported cancer risks nearly ten times larger than those attributed to ETS.

EPA FAILED TO STATE THAT ITS RANGE OF RISK ESTIMATES SHOULD INCLUDE ZERO, OR NO RISK AT ALL

Thus, EPA's claim that ETS causes some 3000 lung cancer deaths a year is a political conclusion shored up by an assumed identity, unwarranted assumptions, selective use of data, artful statistical manipulations, and the contrived illusion of mathematical

precision. On scientific grounds, a zero excess of lung cancer is just as tenable as -- if not more tenable than -- EPA's creations. Indeed, in a separate and less known document the EPA states:

> "Our best estimate is about 3000 deaths a year. While the true number may be higher or lower, the totality of the evidence and especially the groups receiving the highest exposure levels strongly argue that the number is greater than zero." (7)

In fact, only by artificially increasing the stability of the data and ignoring contrary evidence could the EPA make this statement, because the "totality of the evidence" is also compatible with numbers less than zero.

My purpose here is not simply to cast aspersions on ETS studies, but rather to illustrate how contradictory and essentially uninterpretable are the results if analyzed comprehensively in a true "weight of evidence" exercise. In fact, the "weight of evidence" of which the EPA report speaks is nothing but an exercise in selective use of data, and therefore not "weight of evidence" at all.

EPA'S ARBITRARY PROCEDURES REPRESENT A TREAT TO FREEDOM IN A DEMOCRATIC SOCIETY

We may ask: why is the agency doing this? Its immediate interests involve expanding the support for an army of employees, and reinforcing the personal and political fortunes of its management and its many influential advocates. Since the Agency itself was funded because of public concern, it must keep stoking the fires of fear. As former Administrator Reilly's expert panel noted in its critique of EPA science, "The legal process fosters the presentation of the extremes of scientific opinion." We cannot forget EPA's periodic, costly, but exaggerated reports about ethylene dibromide, Alar, dioxin, environmental asbestos, radon, and other toxic contaminants of food, air and water.

Even among the scientists who reviewed the EPA report there are those whose scientific writings reflect disagreement with the report's conclusions, although they apparently feel the need to agree in public with an Agency that influences much of the research funding they obtain (8). EPA and its associates must believe that the end justifies whatever means in the crusade against tobacco. But who could feel safe if such an attitude were condoned? In the end, who will control the controllers?

Tobacco and smoking may indeed be legitimate public health issues, but the ETS report does not rest on firm scientific ground. The EPA report on ETS flies in the face of the standards of conduct that all scientists are required to observe.

A regulatory agency does not fulfill the public's expectations of due process if it operates under its own rules on the basis of unwarranted assumptions. In an open society such an agency should not be allowed to act arbitrarily. At the very least, it should be required to obey generally accepted norms of scientific evidence and conduct: norms that are independently justified by their transparent and rational fairness, and their timeless ethical values.

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U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON AGRICULTURE
SUBCOMMITTEE ON SPECIALTY CROPS
AND NATURAL RESOURCES

STATEMENT OF MAURICE LEVOIS, PH.D.
ON THE EPA ETS RISK ASSESSMENT

Mr. Chairman, my name is Maurice LeVois. I am the principal scientist in Environmental Health Resources, an association of consulting epidemiologists and statisticians with offices in Mill Valley, California. I was formerly Director of the Veterans Administration Office of Agent Orange Research and Education, and a scientist in the Agent Orange Study Unit at the Centers for Disease Control.

I have been asked by The Tobacco Institute to submit testimony summarizing my views on the manner in which a recent risk assessment by the Environmental Protection Agency treated the issue of exposure to environmental tobacco smoke (ETS) and its possible relationship to lung cancer. As detailed below, in my judgment the EPA document has numerous basic flaws and cannot be relied on as an estimate of ETS-related risk.

Spousal smoking is a biased definition of ETS exposure.

A fundamental problem with ETS epidemiologic data is that all of the studies use spousal smoking as the basic definition of ETS exposure. To complicate matters further, spousal smoking is not objectively measured. Instead, spousal smoking data are actually the subjective responses to questionnaires of study subjects, and in most studies surrogates for deceased subjects. Spousal smoking is not just an imprecise definition (i.e. resulting in nondifferential misclassification of exposure); it is also biased.

It is generally recognized that the spousal smoking definition leads to selective misclassification of active smokers. Since spouses of smokers in ETS studies are more likely to be current or former smokers themselves, the spousal smoking study design produces a biased estimate of the association of lung cancer and ETS exposure. Attempts at *post hoc* correction for possible effects of smoker misclassification, such as employed by the EPA in their ETS risk assessment, are not based upon sound data. The assumptions employed in such exercises simply reflect the biases of the authors. *Post hoc* correction cannot be regarded as an acceptable substitute for employing an unbiased study design.

In addition, the spousal smoking definition of ETS exposure confounds many lung cancer risk factors (such as socioeconomic status, prior lung disease, diet, and occupational exposure) that are shared by spouses and are known to be more common in households where there is a smoker.

Biases introduced when spousal smoking is employed as a proxy

for ETS exposure could easily be responsible for the very weak pooled spousal smoking / lung cancer association reported by EPA. It is noteworthy that meta-analysis of results of studies that have looked at ETS exposure in the workplace (as opposed to using spousal smoking as the ETS exposure definition) shows no increase in ETS related lung cancer risk. This important discrepancy undermines both the validity of the spousal smoking proxy and the inference that ETS exposure causes lung cancer.

Meta-analysis compounds bias in ETS epidemiologic data.

Meta-analysis (or pooling) of ETS epidemiologic data cannot correct for biases introduced by the spousal smoking definition of ETS exposure. Meta-analysis can, however, make the effects of biases introduced by the spousal smoking study design appear statistically significant. Because the individual ETS studies are flawed, meta-analysis of these studies is not a valid approach to ETS risk assessment. Despite the problems of bias and confounding, EPA has relied exclusively on meta-analysis of spousal smoking epidemiologic data, and numerous related assumptions, to arrive at their ETS / lung cancer risk estimate.

Multiple comparison bias.

Because both ETS exposure and lung cancer are often defined in a variety of ways in a single study, there is often a question as to the meaning of inconsistent or contradictory results. For example, in a single study the researchers may define 'ETS exposure' as: ever- versus never- exposed to ETS as a child, as a spouse, or in the workplace; as years of childhood, spousal, or

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workplace ETS exposure; as the average number of packs of cigarettes smoked by parents, spouse, or co-workers; as 'pack X years' of exposure as a child, spouse, or in the workplace. The researchers will then proceed to run numerous analyses on a combination of these and other definitions derived from looking at multiple lung cancer cell types and/or other subsets of the cases and controls.

When many related significance tests are conducted in a single ETS study, and the results of only one or two of the tests are reported, the nominal significance levels of the results are not valid. In reporting results of ETS epidemiologic studies the authors are usually able to select from among multiple results, and generally ignore the fact that multiple comparisons bias reported significance levels by underestimating the probability that chance alone could explain reported associations.

The EPA report ignores discrepancies and uses ETS data selectively.

EPA estimates that ETS exposure causes 3000 nonsmoker lung cancer deaths in the United States each year (Respiratory health effects of passive smoking: Lung cancer and other disorders; EPA 1992). This estimate is based on a meta-analysis of data from a subset of epidemiologic studies on the lung cancer risk in nonsmoking women with spouses who smoke. EPA omits data from the largest U.S. studies, does not employ epidemiologic data for males, any animal data, or dosimetric data to derive, or to cross-validate, its risk estimate. If the ETS epidemiologic studies are

uncritically accepted, then the U.S. population risk estimate is largely determined.

Given the central importance of the underlying epidemiologic data, one would have expected EPA to review critically the epidemiologic studies to determine whether they provide an adequate basis for drawing the inference that ETS causes lung cancer. Instead, the EPA report provides a highly selective review of the issue of epidemiologic causation, essentially ignoring conflicting data and conclusions reached by skeptics, including the International Agency for Research on Cancer (IARC, 1987) which found that the ETS epidemiologic data do not adequately support a causal inference.

Interpreting the epidemiologic evidence of health effects possibly associated with ETS exposure involves the most difficult methodological issues in epidemiology (weak associations, indirect and unreliable measures of exposure, extremely low level exposures, long latency periods, and numerous possible sources of bias and confounding). It is not possible to use ETS epidemiologic evidence in a risk analysis without making countless sophisticated epidemiologic judgments.

An EPA Workshop Report strongly advised EPA that the Agency is currently not in a position to assert expert judgments on medical and epidemiological matters, noting that: "EPA needs additional experienced epidemiologists to evaluate epidemiologic data and to assist in risk assessments, because professionally sophisticated judgments are required when evaluating the studies." (EPA Workshop

Report, 1989; p.16).

If EPA wishes to render judgments on the adequacy of epidemiologic study data and the strength of causal inferences drawn from human evidence, then EPA's failure to follow the recommendations of its own work group, and the failure of this EPA risk analysis to apply rigorously the criteria set out in the agency's Workshop Report, are serious deficiencies that set a very poor precedent.

Interpreting weak epidemiologic associations can be exceedingly difficult, requiring not only accurate and precise exposure and disease data, but adequate control over the effects of possible biasing and confounding factors (Wynder, 1987). The present EPA risk analysis fails to apply basic scientific standards of criticism to the ETS epidemiologic studies, presents only information that is consistent with the EPA's hypothesis of causation, and depends on the omission of pertinent information to draw its conclusions. This is not the type of "epidemiology" that EPA, or any other agency, should be practicing.

The EPA document presents vigorous arguments in support of its conclusions, and minimizes or ignores data and arguments inconsistent with its conclusions. This unscientific approach undermines the scientific credibility of the EPA's ETS risk assessment.

For example, the use of less stringent one-sided statistical tests, which are almost never justified in biomedical research -- especially when interpreting weak epidemiologic associations -- is

clearly result oriented and unscientific. So too is EPA's use of an unpublished method to "adjust" for smoker misclassification -- one that relies on the weakest and most optimistic data available -- in order to trivialize valid concerns about the effects of misclassification bias. The result orientation of the draft is also seen in its reliance on circular arguments to justify conclusions, such as the argument that unreliable measures bias ETS results toward the null hypothesis, which is only true if one *assumes* a true ETS effect, and the circular argument used to justify a background "adjustment" which first *assumes* a true ETS effect, and then triples it! Even assuming a true ETS effect, these "adjustments" would be purely speculative and unscientific. Such adjustments render the report's subsequent discussion of uncertainty pure fiction.

The result orientation of the EPA's ETS risk analysis is also clearly demonstrated by their inappropriate use of a one-tailed, 90% significance test for their meta-analysis (the central analysis used by EPA to estimate an ETS/lung cancer risk). The first draft of the EPA's ETS risk assessment used a two-sided significance test for the main spousal smoking analysis. Had the same two-sided significance test been used in the revised EPA risk assessment the result would not have been statistically significant. In their final risk assessment the EPA shifted to a one-sided statistical test. It is clear from this shift that the EPA decided to use a one-sided significance test after reviewing the data and observing that a two-sided test did not achieve statistical significance.

Here is what some highly respected biostatisticians have to say about the use of such tests:

J.L. Fleiss - "By performing a one-tailed test, [the researcher] is ruling out as unimportant the possible inference that p_1 (the rate of disease in the control group) is significantly greater than p_2 (the rate of disease in the exposed group)."

Page 20.

"...a one-tailed test is called for only when the investigator is not interested in a difference in the reverse direction from that hypothesized."

Page 21.

"If, however, the investigator intends to report his results to his professional colleagues, he is ethically bound to perform a two-tailed test."

Page 21.

Joseph L. Fleiss. Statistical Methods for Rates and Proportions. New York: John Wiley & Sons, 1973.

P. Armitage - G. Berry "The critical value for a one-sided test at level P is therefore the same as that for a two-sided test at level $2P$. In a sense the distinction is semantic. On the other hand there is often a temptation to use one-sided tests rather than two-sided tests because the probability level is lower,

> and therefore the apparent significance is greater. A decision to use a one-sided test should *never* be made after looking at the data and observing the direction of the departure. Before the data are examined one should decide to use a one-sided test only if it is quite certain that departures in one particular direction will always be ascribed to chance, and therefore regarded as nonsignificant however large they are. This situation *rarely* arises in practice, and it will be safe to assume that significance tests should almost always be two-sided." Page 98.
>
> P. Armitage and G. Berry. Statistical Methods in Medical Research. 2nd ed. Oxford, England: Blackwell Scientific Publications Ltd, 1987.

The EPA has done exactly what Armitage and Berry warn against. They have chosen a less stringent one-sided test after observing that a standard two-sided test did not achieve statistical significance. The 90% confidence level used in EPA's ETS risk assessment would not be accepted by that Agency if it were, for example, submitted by a manufacturer as part of an application for an EPA regulated pesticide. A one-in-ten error rate is simply not good enough, and should not have been used in the EPA's ETS risk assessment.

Prior to release of the EPA document new spousal smoking data

were published that brought the pooled lung cancer risk estimate down even further, to a level that would not be significant at even the 90% confidence level. Such statistical instability plainly contradicts EPA's claim of medium to high confidence in their ETS risk estimate, and underscores the need for higher scientific standards than they have employed.

Tests of statistical significance are valid aids in decision-making only if the underlying data are unbiased. The error EPA made by employing a one-sided, 90% significance test should not obscure a more basic and important error. The EPA has pooled results from spousal smoking studies that are not adequate to answer questions about possible health effects of ETS exposure. These studies attribute all of the reported spousal smoking / lung cancer risk to ETS exposure, even though it is clear that this risk estimate is biased by a host of other lung cancer risk factors introduced by the spousal smoking design. The EPA's ETS meta-analysis simply pools biases contained in the individual studies to produce a biased result.

Conclusion.

There are fundamental flaws in the EPA's ETS risk assessment. The ETS epidemiologic data are derived from flawed spousal smoking study designs. Meta-analysis of biased spousal smoking study data compounds the effects of bias, and is not a valid methodology for ETS risk assessment. Recent contradictory study results have been ignored by EPA, as have the contradictory data from studies of ETS

exposure in the workplace which do not show a risk elevation. The use of one-sided, 90% significance tests after viewing the data and observing that use of the standard two-sided, 95% confidence level would not produce a significant result, is contrary to accepted statistical methodology and reflects a clear bias in favor of statistical significance at the expense of stability and confidence. The EPA's ETS risk assessment should not be relied upon as an unbiased estimate of the risk of ETS exposure because it exploits flawed data and employs biased, unscientific methods.

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HOUSE COMMITTEE ON AGRICULTURE
SUBCOMMITTEE ON SPECIALTY CROPS AND NATURAL RESOURCES

STATEMENT OF MAURICE E. LEVOIS, PH.D.

Mr. Chairman, my name is Maurice LeVois. I am the principal scientist in Environmental Health Resources, an organization of consulting epidemiologists and statisticians in San Francisco, California. At the request of The Tobacco Institute, I have submitted a written statement to the Subcommittee, in which I set forth some of the reasons why I believe that the recent risk assessment on environmental tobacco smoke by the Environmental Protection Agency is fundamentally flawed. I would like to amplify my written statement today by briefly discussing a recent scientific conference that I attended.

A very well attended symposium on meta-analysis was held at the Annual Meeting of the Society for Epidemiologic Research in Keystone, Colorado, on June 16-18, 1993. The discussants were Drs. Sander Greenland of the UCLA School of Public Health, Diana Petitti of the University of California at San Francisco, and Samuel Shapiro of the Sloan Epidemiology Unit. All three discussants agreed that meta-analysis of epidemiologic data is essentially useless as an aid to drawing causal inferences from epidemiologic studies reporting weak associations, i.e., relative risks of less than about 2.0, because it is impossible to exclude bias and confounding as alternative explanations. They further agreed that most meta-analyses of epidemiologic data appear to be aimed at cutting

off debate and stifling further study of controversial topics, rather than at highlighting differences and discrepancies among the studies and seeking improved research methods.

All three discussants expressed concern that meta-analysis abuses are becoming increasingly common in epidemiology, and that up to the present time there has been little or no critical review of this problem.

Although the discussants were chosen in the hope that there would be a lively debate on the topic, the discussants noted that their disagreements, if any existed, were largely peripheral, relating to what role, if any, meta-analysis should play in interpreting epidemiologic results. The published abstract of Dr. Shapiro's comments, entitled "Meta-Analysis, Shmeta-Analysis," indicates how negative these discussants were on this topic. I quote:

> "In the past decade there has been an explosive growth in the application of meta-analysis to published observational data, mainly in order to confer statistical stability to relative risk (RR) estimates of low magnitude (<2.0). In theory, systematic biases across published studies (including the selective publication of positive results), and of shared confounding, cannot be eliminated by meta-analysis. In practice, there are commonly strong grounds for inferring shared biases or confounding. Even the decision to

undertake a meta-analysis may be biased. For RR estimates of low magnitude rendered statistically stable by meta-analysis, it still remains beyond the resolving power of nonexperimental research to distinguish between bias, confounding, and causation. Additional defects of meta-analysis are esoteric impenetrability of the data; ex-cathedra judgements (or no judgements) of the quality or validity of the individual studies; discouragement of further research; encouragement of exaggerated claims; and the generation of a new Ph.D. industry. The use of meta-analysis in observational research should be abandoned."

The EPA's ETS risk assessment, with both its causal inference and risk estimate based upon meta-analysis of a collection of weak epidemiologic studies, is a striking example of the misuse of meta-analysis. Only the generation of new Ph.D.s is lacking.

That concludes my statement, Mr. Chairman. I would be happy to answer your questions.

ASSIST
American Stop Smoking
Intervention Study
for Cancer Prevention

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July 21, 1993

Honorable Members of the U.S. House of Representatives
Agriculture Committee
Subcommittee on Specialty Crops

Dear Honorable Members,

Virginia ASSIST is a coalition of 23 community organizations in Virginia working together to decrease the illness caused by tobacco. We urge that the EPA report be accepted as the state of the art of medical thinking regarding the health effects of environmental tobacco smoke.

Tobacco smoke often causes disease in the smoker - it can also cause disease in innocent bystanders. The scientific and medical literature is packed with evidence that tobacco smoke causes disease. **There is no legitimate controversy about this.** There are over 4000 chemicals in tobacco smoke, many of which are proven to cause cancer and other deadly diseases in humans, and the law requires the government to protect our citizens from cancer causing chemicals in the workplace and in public places. Tobacco smoke is carcinogenic and people who don't choose to breathe it should be protected by law from being forced to do so.

There are more than 20 scientific studies showing that exposure to environmental tobacco smoke increases the risk of developing serious diseases including lung cancer, and the fact that not all studies agree in their findings is to be expected. Taken as a whole, these studies show that regular long term exposure to environmental tobacco smoke can kill people. Not only is this scientifically valid, but it agrees with common sense. If people go on breathing poison year after year, some of them will die from it, and tobacco smoke is poison.

We in Virginia ASSIST are a diverse group working together to improve the health of our citizens, by reducing the terrible burden of suffering and health care expenses caused by tobacco. Please do not allow paid spokepeople from the tobacco industry to erase the gains made by publication of the EPA report.

Sincerely,

Kevin R Cooper, MD

Kevin R. Cooper, M.D.
Professor of Medicine
Chairman, Virginia ASSIST

AMERICAN CANCER SOCIETY

VDH

NATIONAL CANCER INSTITUTE

Funding for the ASSIST Project is provided through the National Cancer Institute.

WRITTEN COMMENTS OF THE

BUILDING OWNERS AND MANAGERS ASSOCIATION (BOMA) INTERNATIONAL

ON ENVIRONMENTAL TOBACCO SMOKE

SUBMITTED TO THE

SUBCOMMITTEE ON SPECIALTY CROPS AND NATURAL RESOURCES

HOUSE AGRICULTURE COMMITTEE

JULY 21, 1993

The Building Owners and Managers Association International
1201 New York Avenue, NW, Suite 300
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202-408-2684

Second-hand smoke in the workplace is a growing concern for building owners and managers across the country. The Building Owners and Managers Association (BOMA) International appreciates the opportunity to submit comments to the subcommittee.

Americans spend the majority of their day indoors, and building owners and managers have a responsibility to their tenants to provide and maintain healthy indoor air.

A healthy indoor environment is a marketplace concern, important in attracting and retaining tenants. Increased media and legislative attention, however, has caused this to become a higher profile issue in recent years. Reliable information is needed to address this situation effectively and responsibly. BOMA members have long pushed for research on the sources of, and contributors to, indoor air quality problems -- and we are adamant about the need for good guidance.

BOMA International has worked with industry groups and government agencies in developing our efforts on indoor air quality. We have also implemented a strong campaign to distribute sound guidance to improve the indoor air quality management programs in the commercial property community. In cooperation with the EPA and our local associations around the country, we have held a nationwide series of over 50 seminars based on the EPA manual Building Air Quality.

The Environmental Protection Agency's classification of second-hand smoke as a "Class A" carcinogen further emphasizes the responsibility of building management to protect the health of office building tenants, their employees, and their guests and clients who may be exposed to this known carcinogen.

Second-hand smoke has long been considered a severe nuisance to non-smokers, and has been a suspected health hazard for some time as well. EPA's confirmation of tobacco smoke as a known carcinogen merely corroborates what we have suspected for some time. This finding also makes it imperative that building owners and managers take steps to protect their tenants from this indoor air health hazard.

Indoor air quality problems may be prevented through a combination of management practices -- maintaining the filtration and ventilation systems, bringing in adequate outside air, and controlling the contaminant sources. In buildings that do not have separate ventilation systems for designated smoking areas, second-hand smoke is distributed into non-smoking areas of the building, endangering the well-being of non-smokers. Most office buildings do not have separately ventilated smoking areas.

BOMA firmly believes that the most effective course of action is to prevent contaminants from being introduced into the workplace in the first place. Second-hand smoke is one of the leading contributors to indoor air pollution, and banning smoking in the workplace would significantly improve the quality of the air we breathe.

In January, BOMA International's Board of Governors unanimously passed a resolution to support a federal ban on smoking in the workplace. We see this resolution as a responsible and pragmatic step forward.

In conclusion, second-hand smoke is one of the primary contributors to indoor pollution and a serious health hazard. Building owners and managers have a responsibility to their tenants to protect their indoor environment. BOMA International will continue to educate building owners, managers, and tenants on the health risks and recommend that the federal government implement a smoking ban in the workplace.

* * *

Founded in 1907, the Building Owners and Managers Association (BOMA) International is a dynamic federation of 98 local associations whose members own or manage over 7 billion square feet of commercial properties and facilities in North America. The membership -- comprised of building owners, managers, developers, leasing professionals, facility managers, asset managers and the providers of goods and services -- collectively represents all facets of the commercial real estate industry. BOMA is firmly established as the respected resource on national matters affecting the industry, such as the Americans with Disabilities Act (ADA), Indoor Air Quality (IAQ), the phase-out of chlorofluorocarbons (CFCs), passive loss rules, and more.

Virginia Group to Alleviate Smoking in Public, Inc. GASP[R]
P.O. Box 38134 Richmond, Virginia 23231 804-795-2006

"... to know that even one life has breathed easier because you have lived -this is to have succeeded." R.W. Emerson

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STATEMENT BY: Anne Morrow Donley, Executive Director *Virginia Group to Alleviate Smoking in Public, Inc.*, for U.S. Congressional Hearings, Wednesday, July 21, 1993.

"NONSMOKERS, AND OTHER TOBACCO VICTIMS,
pause in your rage against injustice and feel sorry for the poor little rich tobacco executives. After years of knowingly creating a dangerous product, which used as intended will kill about one out of every three of its consumers, and murder 53,000 bystanders each year in the U.S.A. alone, the tobacco industry faces actual government regulation of where the toxic polluting product may NOT be used - around people who dare to breathe in public.

Imagine, tobacco may have to be treated like other addictive drugs or life-threatening items.

But a wealthy industry with no scruples never gives up in the fight against truth and health. These flat-earth society types managed to stack the EPA Science Advisory Board with several people who have strong ties to tobacco, they even offered million dollar grants to board members, **but the board still came out nailing secondhand smoke as a killer and Group A carcinogen.** Now ***tobacco's bullies*** are again reverting to strong-arm tactics: (1) harassing the Environmental Protection Agency at taxpayer expense, and intimidating scientists along the way, (2) fighting confirmation of President Clinton's choice for Surgeon General, and (3) increasing economic blackmail on businesses. [See attachments of Philip Morris letter to businesses, and partial list of economic blackmail.]

"Therefore, the tobacco executives - many of whom do not smoke or spit their own products - have filed a frivolous lawsuit forcing the government to use tax dollars to defend science and truth. Tobacco's two faithful water boys, Charlie Rose and Tom Bliley, are working with tax dollars to try to subvert truth Congressionally. Bliley has held several meetings reminiscent of Joe McCarthy, questioning the EPA staff on their writing, typing, researching the report on secondhand smoke. Rose has now convened a Congressional hearing (tax $$$) to investigate the scientific procedures used in making the report. **Rose's staff is quick to maintain that Rose has been wanting to call this hearing ever since the report was publicly released in January, and the timing has nothing to do with the confirmation hearings for Surgeon General or tobacco's lawsuit against the EPA.** Rose's staff has said that if Rose is not satisfied with the answers he gets, there will be a series of hearings.

Why is the EPA forced to testify when all of this is under litigation?

The tobacco industry is only satisfied with one thing - profit at any cost, regardless of who pays.

When will the people have a hearing to investigate tobacco influence on public policy?

"It's time this country had a Congressional hearing and investigation for the people, by the people, and of the people, and not for the benefit of greedy tobacco drug pushers, the firm that's wasting taxpayer money to keep smoke rape and harassment legal in this country. Nothing in the U.S. Constitution guarantees even legal drug pushers the right to force everyone to breathe the deadly byproducts against their will. Secondhand smoke is invasive, life-threatening, and unpopular. The tobacco industry is the only group demanding public smoking.

"Secondhand smoke is the third leading cause of preventable death in this country, killing 53,000 Americans EACH year of secondhand smoke related illnesses, but it's still legal to smoke inside government buildings, schools, around children, and in the workplace. An executive order, and acts of Congress could make REAL drug-free zones in schools and elsewhere.

"There is public behavior and private behavior.
Smoking should be done only in private, among consenting adults.
Smoking has no place in schools, the workplace, nursing homes, bowling alleys, restaurants, skating rinks, stadiums, airports, transportation, government buildings, in any place that people are accessing.
Real health reform begins with required and enforced NO SMOKING in all of these places.

**"The smoker may have the legal choice to drug,
but no smoker should have the legal right to hurt another person.**

**"Without any scientific studies, *the Nose Knows* that secondhand smoke hurts.
The studies reveal that secondhand smoke is a killer.**
The EPA Report is only one in a series of reports [National Academy of Sciences, Surgeon General, National Institute of Occupational Safety and Health, etc.] of the dangers of secondhand smoke to the healthy nonsmoker - including children.

"Tobacco may be number one on some lists, but it still smells like number two."

Statement of W. Gary Flamm, Ph.D.
to the House Agriculture Committee Subcommittee on
Specialty Crops and Natural Resources

I hold a Ph.D. in medical biochemistry and am a Fellow and past President of the American College of Toxicology and immediate past President of the International Society for Regulatory Toxicology and Pharmacology. I spent over twenty-five years with the U.S. Public Health Service, where my tenure was divided between the National Institutes of Health and the Food and Drug Administration (FDA). Prior to my retirement from government service in 1988 I was Director of the FDA Office of Toxicological Sciences.

I also served for eleven years as chairman of FDA's Cancer Assessment Committee (CAC), which was responsible for evaluating carcinogenicity data on food ingredients and contaminants, cosmetic formulations and ingredients, and

animal drug residues. The CAC is responsible for deciding whether the available scientific data supports a determination that a particular compound is a carcinogen.

My testimony today draws on my experience of more than a decade as the founding chair of the CAC; several hundred compounds were evaluated for possible carcinogenicity during this period. I have been asked by The Tobacco Institute to present comments on the Environmental Protection Agency's recently released risk assessment on environmental tobacco smoke (ETS) in light of this experience. The views I will express are, however, entirely my own.

INTRODUCTION

I submitted extensive comments to EPA on the two occasions on which the ETS risk assessment was opened to limited public comment. In both of my reviews of the draft reports, I concluded that the totality of data on ETS and lung cancer did not support the claim that exposure to ETS is causally associated with an increased incidence of lung cancer in the United States. I further stressed that the lack of animal studies to support a causal association between ETS and lung cancer, along with other "weight-of-the-evidence" considerations, demonstrated that there is no scientifically valid basis for conducting a risk quantitation on ETS or

classifying ETS as a known, probable, or even possible human carcinogen.

In my reviews of the draft reports I also pointed out that, in order to maintain consistency, EPA should compare its evaluation of ETS with other contemporary evaluations performed by the agency, particularly with the evaluation of the numerous studies on electromagnetic fields (EMF) and cancer contained in an EPA document entitled "Evaluation of the Potential Carcinogenicity of Electromagnetic Fields, Workshop Review Draft." This suggestion is consistent with recommendations made by the Expert Panel on the Role of Science at EPA in its March 1992 report, "Safeguarding the Future: Credible Science, Credible Decisions." The Panel recommended (p.38) that "EPA should examine how the Agency used science in the past in developing one or more regulations."

In my testimony today I shall reiterate and expand on these topics.

GENERAL COMMENTS

The final version of the ETS risk assessment took a somewhat different approach from the first draft issued in 1990. In the first draft, EPA acknowledged weaknesses in individual epidemiologic studies of the reported association between ETS and lung cancer. It also acknowledged weaknesses

in the entire database but concluded, based on meta-analysis (that is, pooling) of the results of the epidemiologic studies, that the studies pointed to a positive association, with the statistical standard of confidence being 95%. EPA did not, in its first draft, attempt to use active smoking data as a basis for concluding that ETS should be classified as a human carcinogen.

In the final risk assessment document, EPA has dropped its caveats, reduced the statistical standard, and ignored important recent studies. The agency now asserts that the epidemiologic studies of ETS unequivocally support a causal link between ETS and lung cancer. It further asserts that ETS is sufficiently similar to mainstream tobacco smoke that ETS can be declared a human carcinogen based solely on studies of active smoking.

In order to conclude that the epidemiologic studies support its contentions, EPA chose to use 90% as opposed to the standard 95% confidence intervals, although it had used the latter standard in the first draft of the document. In other words, the authors of the draft report significantly weakened the scientific standard traditionally used to determine the confidence that could be placed in statistical data.

No reasons were given for this departure from convention, leaving the reader to assume the only basis for applying the 90% rather than the 95% confidence interval was

to allow the authors to declare more studies as positive. By claiming, as the subject report does, that more epidemiologic studies are supportive of causal association, the authors were able to assert that the studies are consistent and that a weight-of-evidence evaluation justified a Group A, or "known human," classification. The fact that novel and unconventional approaches were used in the analysis of the data was ignored.

I can discern no reason for such a change except a desire to support a predetermined policy position. This judgment is underscored by EPA's refusal to consider the results of two important ETS studies--including the largest study yet conducted in the United States. When the data from these two studies is added into the overall data base, the pooled result is statistically non-significant, even if the lax 90% standard used by EPA is applied. Proceeding in this fashion has nothing to do with the application of good science and is contrary to EPA's own 1986 Guidelines for Carcinogen Risk Assessment.

The authors of the draft report also claimed that information on the chemical similarities of mainstream smoke (MS) and ETS and evidence of ETS uptake in nonsmokers is sufficient by itself to establish ETS as a known human lung carcinogen. The contention that MS and ETS are similar is, however, based on fragmentary information. Over 4,000 substances have been detected and measured in MS while only a

handful of substances have been studied in ETS. This obvious difference is ignored in the report. While some overlap exists between MS and ETS, to state categorically that the substances are sufficiently similar to justify a Group A classification is without scientific merit.

Specifically, to suggest that ETS is a human carcinogen based on the identification of components that are themselves regarded as animal carcinogens is contrary to EPA's past policies. According to EPA's classification scheme, in order to justify a Group A designation there must be adequate human data establishing the carcinogenicity of the substance. EPA has to date listed only 14 substances or mixtures of substances as Group A carcinogens. It has never included mixtures solely because they are thought to contain Group A carcinogens as components. In fact, EPA has consistently declined to proceed in this fashion. For example, the agency determined that alpha-napthylamine could not be listed as a Group A carcinogen even though it is known that this compound contains beta-napthylamine, which itself is listed as a Group A carcinogen.

EPA's action sets a peculiar precedent indeed. If it were possible to classify one agent on the basis of its similarity to another agent, diesel exhaust emissions should be classified today as a Group A carcinogen, in that diesel exhausts contain many of the same compounds that are present in coke oven emissions, which in turn are classified by EPA as

a Group A carcinogen. EPA has done no such thing with respect to diesel exhaust emissions. Why did the agency treat ETS differently?

EPA'S RISK ASSESSMENTS FOR ETS, ELECTROMAGNETIC RADIATION AND DIESEL EXHAUST EMISSIONS: A COMPARISON

A. Electromagnetic Radiation

The epidemiologic data base used by EPA to claim that ETS is a Group A carcinogen consists of studies that reported relative lung cancer risks for never-smoking women with smoking husbands as compared with never-smoking women with non-smoking husbands. The EPA guidelines for carcinogen classification provide that in order to classify a substance as a known human carcinogen, sufficient epidemiologic evidence must exist. The first key element in establishing sufficiency is that the epidemiologic studies should consistently report an increase in risk. Implicit in this notion is that the studies, individually and when combined in some summary analysis, report statistically significant increases in risk.

Compare the epidemiologic database on spousal smoking and lung cancer with that for electromagnetic radiation (EMF) and adult cancer. For spousal smoking, EPA

considered 30 studies, only 6 of which reported statistically significant results. The highest relative risk reported in the spousal smoking studies was 2.55 (in a Japanese study that was not statistically significant). In EPA's uncompleted risk assessment of EMF, by contrast, the agency considered 42 studies reporting data on EMF exposure and cancer in adults, with 25 reporting a statistically significant result. See Table 1. The highest relative risk involved in the EMF studies was a statistically significant 13.1 (in a study of utility workers).

Not only are there far more statistically significant epidemiologic studies for EMF, there is also a much higher percentage of studies reporting statistical significance, and the relative risks reported are generally much higher than with ETS. I note in this connection that the magnitude of the relative risk is very important. Many epidemiologists are of the view that it is extremely difficult to ascertain real, non-spurious associations in studies that report relative risks lower than 3.0. Yet, EPA claims that the ETS epidemiology is sufficient and that the EMF epidemiology does not even justify the conclusion that EMF exposure is "probably" (Group B) or even "possibly" (Group C) carcinogenic.

The striking disparity in EPA's treatment of ETS and EMF is highlighted by a review of the EPA report "Electric and Magnetic Fields: An EPA Perspective on Research Needs and

Priorities for Improving Health Risk Assessment" (December 1992). In this document EPA reviews the EMF data and details areas where data is insufficient and where further research is required in order to reduce uncertainties.

EPA criticizes the lack of exposure measurement in the epidemiologic studies of EMF, and states that "[e]xposure data are needed for statistically valid population estimates" and that "[e]pidemiological research and exposure assessment research must be integrated." Not one of the ETS epidemiologic studies measured actual ETS exposure. Yet, EPA completed a full risk estimation including the quantitation of U.S. lung cancer incidence supposedly associated with ETS.

EPA stated in the agency's EMF research priority document that "[e]pidemiological studies on the effect of EMF should be designed to identify and evaluate other factors which may distort the measure of association with EMF exposure." In the ETS risk assessment, EPA dismissed the possibility of such "confounding factors," primarily by merely asserting that the existing studies did not reveal such factors. This is entirely unsatisfactory, since few of the ETS studies ever attempted to account for confounding factors in the first place. Why should EPA request further epidemiologic data for EMF but state that the ETS epidemiologic data is sufficient to claim causality with lung cancer?

EPA also stated that for EMF research "[e]pidemiologic cancer studies should emphasize identification of distinct cancer types." The ETS database is highly inconsistent on this issue. Within the few studies that did separate lung cancer type, some report associations with adenocarcinoma and others with a very different type, small cell cancer. This anomaly calls into question whether all of the cases in a study could reasonably be attributed to a single cause, be it ETS or anything else. EPA practically ignored these inconsistencies in its ETS risk assessment, yet called for further research with EMF.

B. Diesel Exhaust Emissions

EPA also reviewed the epidemiology of diesel exhaust emissions. There are 29 epidemiologic studies that have considered the association between exposure to diesel engine emissions and lung cancer. Eight of the studies report statistically significant results. See Table 1. The highest reported relative risk was a statistically significant 2.67. Yet, EPA wrote in a Workshop Review Draft in 1990 that "[c]ollectively, the epidemiologic studies show a positive association between diesel exhaust exposure and lung cancer. However, because of uncertainties due to lack of actual diesel exhaust exposure data in these populations, the evidence for carcinogenicity of diesel engine emissions in humans is

considered to be limited. This means that a causal interpretation is credible, but alternative explanations such as chance, bias or confounding factors cannot be ruled out."

In this case, EPA has stated that the epidemiology is insufficient due to lack of exposure data. The method used by the epidemiologic studies to estimate exposure to diesel exhaust exposure is, however, precisely the same as that used with ETS--the responses to questionnaires posed either to the subjects of the study or to surrogates of the subjects. Yet, in the eyes of EPA, the epidemiologic data is sufficient for ETS but not so for diesel exhausts. Such inconsistency on the part of a regulatory agency plainly is unacceptable.

Moreover, in the case of diesel exhausts the EPA stated that "[t]he evidence for carcinogenicity of diesel exhaust in animals is considered to be sufficient based on U.S. EPA cancer assessment guidelines." By contrast, no animal inhalation studies have been able to demonstrate the development of tumors in animals exposed to ETS.

Diesel exhausts are a substance that EPA would be expected to care very much about. EPA can regulate diesel emissions. Most of the U.S. population are exposed every day to diesel exhausts. Why, then, has the EPA effectively given up on its risk assessment of diesel exhausts? The last document from the agency on this risk assessment appeared in 1990. In contrast, the risk assessment of ETS, a substance that EPA cannot regulate, has been the focus of considerable

effort, culminating in what could be described as a rush to its publication in the waning days of the last Administration.

It seems clear that EPA has applied completely different criteria in its analysis of ETS as compared with that used for either EMF or diesel emissions. Such obvious inconsistencies undermine the credibility of the agency. That credibility requires, in my judgment, strict adherence to the recommendations in the report of the Expert Panel on the Role of Science at EPA. Further, the Panel's recommendations are fully consistent with those of a National Academy of Sciences report on "Risk Assessment in the Federal Government: Managing the Process," in which it is stated that scientists conducting a risk assessment must adhere rigorously to the scientific facts and the scientific merits of the matter before them. They should not allow their conclusions to be influenced by policy considerations, because to do otherwise makes a sham of the process, leaves the public ill-served and damages the credibility and effectiveness of the agency.

SUMMARY AND CONCLUSIONS

Perhaps the most frustrating aspect of the ETS risk assessment is the general pattern of mentioning uncertainties as a formality, but then ignoring these uncertainties in drawing conclusions. The authors act as if their only obligation is merely to mention the uncertainty--as though it

were unnecessary to resolve the uncertainty or to factor it into the decisionmaking process. For the reader, this problem is further compounded by the very limited amount of time provided for review and public comment. The uncertainties have been pointed out, but they remain unresolved in the final document.

This is exactly what the Expert Panel on the role of science at EPA expressed most concern about. The Panel stated its concern clearly in its first finding, on page 36 of its report, about how EPA uses science in decisionmaking. The Panel found that EPA has not always ensured that reputable scientific views are well explored and well documented, and that the regulatory process at EPA fosters the presentation of the extremes of scientific opinion. This approach runs contrary to the preferred process of developing consensus within the scientific community. The Panel went on to say that EPA science is perceived by many people, both inside and outside the agency, to be adjusted to fit policy. The Panel firmly stated that such adjustments were improper.

The Panel also found that "The interpretation and use of science is uneven and haphazard across programs and issues at EPA. Conflicting science policies between EPA programs create confusion and a lack of credibility for EPA decisions." Confusion is exactly what is being created by the EPA risk assessment on ETS, given its major inconsistencies with other agency projects.

In summary, the EPA ETS risk assessment reaches conclusions based on unconventional analyses; uses methods that have not been critically reviewed; and ignores important published studies. Uncertainties are not considered in terms of their impact on the conclusions drawn in the risk assessment. In addition, the risk assessment review process has been conducted in an atmosphere that has discouraged outside scientific input and has fostered adjustments of science despite the unequivocal admonition against such practices by the Expert Panel on the Role of Science at EPA. The result has been the dissemination of scientifically unjustified conclusions that are in sharp contrast with other EPA documents.

(Attachment follows:)

Table 1: Comparison of the epidemiologic databases of electromagnetic fields, diesel exhausts, and environmental tobacco smoke and lung cancer

Substance	Number of epidemiologic studies		
	Total	Statistically Significant (95% C.I.)	% Stat. Significant (95% C.I.)
Electromagnetic fields	42	25	60%
Diesel exhausts	29	8	28%
Environmental tobacco smoke	30	6	20%

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July 26, 1993

Congressman Charlie Rose, Chairman
Committee on Agriculture
Subcommittee on Specialty Crops and
Natural Resources
U.S. House of Representatives
Room 1301, Longworth House Office Bldg.
Washington, DC 20515

RE: July 21 Hearing on EPA's Report on Environmental Tobacco Smoke

Dear Congressman Rose:

After attending your well-conducted hearing, I offer the following comments. Please consider entering them into the record.

During the hearing, Dr. Steven Bayard -- the person responsible for the EPA report -- told you and your subcommittee that what really convinced him that ETS is a lung carcinogen were the "trends" in dose-response. In other words, "trends" in some of the studies indicate that the more cigarettes a husband smokes, or the longer a nonsmoking wife lives with a smoking husband, the more her lung cancer risk increases. These "trends" can be found in Table 5-11, Page 5-41, of the EPA's final report (December 1992).

These "trends," however, are not based on measurements of actual exposure to ETS.

In a review draft on electromagnetic fields, EPA said it was *impossible* to do a dose-response analysis without measurements of actual exposure:

> ...no measurements of actual exposure were available in any of these studies. The authors are forced to rely on surrogates, such as employment in occupations that have a potential for exposure to EM fields, without any proof to substantiate if any or how much exposure actually took place. *Under these circumstances it is impossible to do dose-response analyses*. (emphasis added) (Evaluation of the Potential Carcinogenicity of Electromagnetic Fields. EPA Review Draft, October 1990, p. 3-147)

How was it possible, then, for EPA to do a dose-response analysis on ETS? Notice that the studies on ETS are as inadequate as the studies on electromagnetic fields:

> ...potential for bias in all of the analyses...(The Correa Study, EPA Final Report, December 1992, p. A-37)
>
> ...an effect by one or more of these [confounding] factors cannot be ruled out. (The Garfinkel Case-Control Study, EPA Final Report, December 1992, p. A-50)
>
> ... some potential for misclassification and other sources of bias. (The Akiba Study, EPA Final Report, December 1992, p. A-23)

What About Confounders?

Dr. Bayard told you that confounders have been ruled out. This is not true.

The Science Advisory Board said "there is *no way* to evaluate the importance of occupation, radon exposure, and diet as confounders of the ETS-lung cancer relationship, or to adjust for them, since virtually none of the studies contain information on them." (emphasis added) (SAB Report, April 19, 1991, p. 34)

The Science Advisory Board also said that if you're married to a smoker, you could be vulnerable to several things that increase lung cancer risk. Some of those things are lower socio-economic status, diet, alcohol, drugs, and more exposure to air pollution. (SAB Report, April 19, 1991, p. 46)

How do we know the dose-response "trends" are not a reflection of some of those things? One study found that nonsmokers reporting longer exposures to ETS were also more likely to report greater use of alcohol and marijuana, exposure to occupational hazards, and being currently not married. (Friedman et al., 1983. Prevalence and Correlates of Passive Smoking. *American Journal of Public Health*, April 1983, Vol. 73, No. 4)

Because of their finding, Friedman et al. were cautious:

> Our data...indicate that studies of the effects of passive smoking should consider the correlates of this form of smoke exposure before concluding that [ETS] is responsible for some observed effect. Perhaps, for example, the greater alcohol consumption of passive smokers may be at least partly responsible if they experience more time off work. Or, persons with higher degrees of passive smoking may experience a greater frequency of upper respiratory infections not because of the smoke but because they are exposed to more people.

Dr. Bayard says that his report examined potential confounding factors such as history of lung disease, home heat sources, diet, and occupation, and "concluded that none of

- There are no measurements of actual exposure to ETS in the studies used by EPA.

- The authors rely on a surrogate for ETS exposure (the husband's smoking habits).

- Marriage to a smoker provides only a potential for exposure to ETS.

  (One study found that 47% of its nonsmoking female respondents reported zero hours of ETS exposure in the home even though they were married to smokers. [Friedman et al., 1983. Prevalence and Correlates of Passive Smoking. *American Journal of Public Health*, April 1983, Vol. 73, No. 4])

- There is no proof to substantiate how much -- if any -- exposure to ETS actually took place!

The dose-response "trends" Dr. Bayard refers to came from studies riddled with biases and confounders. Here's what EPA says about those studies:

> The high uncertainty associated with this study...renders it potentially misleading to the point that it may be preferable to omit it from the analysis. (The Inoue Study, EPA Revised Draft, May 1992, p. 5-32)
>
> ...influence of biases and confounding cannot be assessed beyond noting that it may be substantial. (The Geng Study, EPA Revised Draft, May 1992, p. 5-31)
>
> ...no attempt to control for major potential confounders, including the fundamental factor of age...(The Lam T Study, EPA Revised Draft, May 1992, p. 5-34)
>
> ...confounding...could have biased results in either direction. (The Gao Study, EPA Revised Draft, May 1992, p. 5-30)
>
> Diet, cooking and heating practices, and occupation were not directly controlled for...leaving open the potential for confounding with either upward or downward effects. (The Fontham Study, EPA Revised Draft, May 1992, p. 5-29)
>
> ...limited exposure information and other potential sources of bias... leave its assessment in question. (The Garfinkel Cohort Study, EPA Final Report, December 1992, p. A-56)

these factors could account for the observed association between lung cancer and ETS." (EPA Final Report, p. 1-10)

On the contrary, most of the studies provided no information on such things. To use these studies as evidence that ETS is a lung carcinogen is a violation of EPA Guidelines:

> The available studies, while showing evidence of association, did not exclude chance, bias, or confounding, and therefore a causal interpretation is not credible. (Guidelines for Carcinogen Risk Assessment. The Risk Assessment Guidelines of 1986, U.S.EPA, p. 1-11)

When the Chairman of the Science Advisory Board, Dr. Morton Lippmann, announced that the EPA revised draft was approved and accepted, he wavered on the issue of confounders. Here's what he said:

> The possibility of confounding has been considered and ruled out. *It's hard to really say they've been ruled out*, but on the other hand again, I see no evidence that confounding is likely to overwhelm the judgment. (emphasis added) (EPA-SAB Meeting, July 21-22, 1992. American Reporters Transcript, p. II-158)

The EPA Guidelines did not ask for Dr. Lippmann's opinion. They specifically stated that the ***studies*** must exclude confounders -- which they did not.

EPA's Use of Unpublished Material

When it comes to rules about using unpublished material, EPA can't make up its mind. First, Dr. Farland tells you that EPA can't use studies unless they've been published. This is his argument for not including the Brownson and Stockwell studies in the EPA's risk assessment.

On the other hand, EPA uses an unpublished method of adjusting the ETS data for "misclassification," apparently because it is "helpful" in establishing ETS as a Group A human carcinogen.

The unpublished adjustment method used by EPA was designed by Dr. Judson Wells, volunteer to the American Lung Association. Dr. Wells' method makes a lower rate of adjustment than the method used in EPA's first draft on ETS in 1990 (the lower the rate of adjustment, the higher the relative risk will be).

Why did EPA drop the adjustment method used in the first draft? The Science Advisory Board approved of that method, saying the issue was "considered in detail" and "appropriate corrections have been made for misclassification." (SAB Report,

Perske 5

April 19, 1991, p. 31)

One of the Science Advisory Board members, Dr. Geoffrey Kabat, is not convinced that the new unpublished method covers all bases. He said:

> The overall relative risk for exposure to spousal smoking in the U.S. epidemiologic studies is 1.19 and for studies from all countries combined may reach 1.4. With a relative risk of this magnitude, it is difficult to rule out effects of bias and confounding which may well operate in the same direction in studies from diverse countries and cultures. *I am not convinced that the adjustment for misclassification of active smokers (particularly long-term ex-smokers) as never smokers is adequate to deal with this major threat to the validity of the epidemiologic studies*. (emphasis added) (Comments on EPA's Draft Report: "Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders." Geoffrey Kabat, Ph.D., July 28, 1992)

EPA cannot have it both ways. Either it can or cannot use unpublished material. If EPA is to be credible it must abide by its own rules. If the Stockwell and Brownson studies were excluded from the risk assessment because they had not yet been published, how can EPA justify using the unpublished adjustment method designed by Dr. Wells?

Congressman Rose, it was mentioned at your hearing that a formal review of the EPA's report may be warranted.

I think you should request such a review.

We have serious health and environmental problems in this nation. ETS is not one of them. The huge efforts and millions of federal dollars being used to keep the pot boiling on exaggerated and unsubstantiated claims about ETS is appalling to me. Under the guise of "protecting" us from a tiny risk that may not even exist, EPA has done damage to millions of lives.

Please know that your efforts and those of your subcommittee and staff are greatly appreciated.

Sincerely,

Martha Perske

cc: Mr. Keith Pitts
Mr. Bo Greenwood

HOUSE COMMITTEE ON AGRICULTURE

SUBCOMMITTEE ON SPECIALTY CROPS

AND NATURAL RESOURCES

A CRITIQUE OF THE EPA REPORT ON ENVIRONMENTAL TOBACCO SMOKE

Paul Switzer, Ph.D.

I am Professor of Statistics and Professor of Applied Earth Sciences at Stanford University where I have taught since 1965, the year of my Statistics Ph.D. Degree from Harvard University. During this period my principal research interests have centered on problems of statistical methodology applied to environmental problems. I have been Chairman of the Statistics Department at Stanford University, have served as editor of the Journal of the American Statistical Association, and served on review panels and committees of the National Academy of Sciences, the Environmental Protection Agency, the American Statistical Association, the Electric Power Research Institute, and others. I am familiar with the published literature on the epidemiology of lung cancer as it may relate to environmental tobacco smoke (ETS) exposure. I have been asked by the Tobacco Institute to present these comments to you; they represent my own opinions and are not

necessarily those of the Tobacco Institute or Stanford University.

INTRODUCTION

In January, 1993, the U.S. Environmental Protection Agency (EPA) released a risk assessment of lung cancer mortality and ETS exposure (1), based on selected previously published epidemiologic studies of spousal ETS exposure combined with assorted assumptions and extrapolations. EPA classified ETS as a "Group A" or "known human" carcinogen. The agency also attributed 3,060 lung cancer deaths annually to ETS among all U.S. non-smokers and former smokers, with an astonishing claim of "medium to high" confidence for this estimate. In my opinion, confidence in this estimate is very low and provides no basis for regulatory action or carcinogen classification.

EPA's claimed high level of confidence takes no account whatsoever of numerous uncertainties that undermine the agency's conclusions. These uncertainties include those involving the effects of selective reporting and confounding biases on the results of the epidemiologic studies, the adjustments applied to the relative risk estimates for individual studies, assumptions regarding the comparability of spousal and the non-spousal ETS exposure, the assessment of

background exposure, the applicability to ex-smokers of relative risk estimates derived from studies of never-smokers and the downward extrapolation of a dose-response function to background levels. Admittedly, many of these sources of uncertainty and error are difficult to quantify, but EPA's reported confidence in its risk estimates, and the risk ranges cited in the agency's report, effectively assume that all of these uncertainties are zero.

CARELESS META-ANALYSIS OF PUBLISHED STUDIES & OMISSION OF RELEVANT DATA

The EPA report calculated a summary relative risk for lung cancer of 1.19 based on a meta-analysis of 11 U.S. studies which compared non-smoking women married to smokers with non-smoking women married to non-smokers. The report also gives a 90% confidence interval in place of the usual 95% which it used in its draft report, thereby creating the impression of a narrower range of possible risk estimates. Furthermore, the method of calculating the confidence interval is optimistic because it ignores any heterogeneity between study populations. Finally, the EPA report used an unadjusted risk number for the Janerich study (8).

It is surprising that the EPA report omitted two recent U.S. studies from its meta-analysis. The studies by Brownson et al. (5) and by Stockwell et al. (3) were available

well before the report was published and significantly affect the overall analysis. The Brownson study is one of the largest ETS-lung cancer studies conducted in the U.S. and it reported a relative risk of 1.00 for spousal smoking, equivalent to no risk elevation. Including these two studies in the meta-analysis, using the adjusted relative risk for the Janerich study, but still ignoring inter-study heterogeneity, gives a summary relative risk estimate of 1.07 with 95% confidence limits of 0.95 to 1.21 -- hardly a convincing basis for policy action.

Meta-analysis is a methodology for combining information from multiple studies to achieve greater precision in the estimation of relative risk. The principal difficulty with a meta-analysis of ETS-lung cancer epidemiologic studies is the same as that associated with the analysis of any observational data. The data for a meta-analysis do not come from a designed meta-experiment, and certainly not a meta-experiment aimed at inference for the U.S. target population. Therefore, as with other observational data, great care must be taken to address sources of bias deriving from the planning, reporting, and selection of studies, how the available data relate to the estimation target, and hidden sources of correlation among the data. EPA failed to address these issues.

THE EPA'S CONJECTURAL ETS EXPOSURE ASSESSMENT OF THE U.S. POPULATION

Whatever the excess lung cancer risk estimate may be for a sufficiently high spousal exposure, the assignment of a positive risk for all other non-smokers, as EPA did, is problematic. The EPA report essentially assigns one risk number to a group of men and women non-smokers and ex-smokers which it defines as having ETS exposure equivalent to female spousal exposure, and a second smaller risk number to all other non-smokers and ex-smokers, called the background exposure risk. The background risk is a calculated quantity based on a low-dose extrapolation of already small numbers obtained from some of the spousal studies together with assumptions regarding the ETS exposure ratio.

However, the EPA estimate of background ETS exposure is subject to substantial doubt since published cotinine studies, used to infer background ETS exposure, have reported highly variable and inconsistent results. In four studies, including the Cummings study (10), the mean cotinine level among subjects reporting no ETS exposure was similar to the mean level for subjects married to non-smokers, which suggests that in both groups a substantial part of these levels may be due to factors other than exposure to ETS, such as dietary sources of nicotine and artifacts of the cotinine bioassay. Nevertheless, the EPA assumed that background ETS exposure was

fully 57% as large as the estimate for spousal exposure and, furthermore, that 60% of unmarried females (and males) had ETS exposures equal to the high spousal exposure level. These assumptions are unjustified.

There are no available epidemiologic comparisons of subjects who received no ETS exposure with subjects exposed to ETS from exclusively non-spousal sources, so there is no direct evidence of ETS exposure from "background" sources being associated with lung cancer risk. However, several studies have reported results on ETS exposure from sources other than the spouse, particularly in the workplace. A meta-analysis of 11 workplace ETS-lung cancer studies shows essentially no risk elevation (11). Furthermore, the two studies which explicitly consider ex-smokers, Varela (9) and Brownson et al. (5), both report no spousal smoking-lung cancer risk elevation, yet the EPA report assumes that the ETS relative risk for lung cancer risk is the same for former smokers and non-smokers with spousal exposure. This assumption is not justified.

STATISTICAL BIAS AND SYSTEMATIC ERRORS IN THE EPA ASSESSMENT

Because the reported relative risks are close to one for most studies of ETS and lung cancer (i.e., no elevation in risk for ETS exposure), serious attention must be paid to

problems of confounding and bias. As in all epidemiologic studies looking for small effects, the sources of bias and confounding can be subtle but far-reaching. It is important to emphasize that a multiplicity of studies does not mitigate these problems. Surprisingly, the EPA report claims that a multiplicity of studies provides protection against bias.

REPORTING BIASES

Reporting biases can include failure to complete studies which do not exhibit early positive findings, reluctance of investigators to submit, and of journals to publish, findings which are not statistically significant and positive, and the early reporting of partially completed studies when they show positive findings. For example, the recently published data of Fontham et al. (2), which figure prominently in the EPA report, were based on an incomplete study. A second example is the omission of detailed results on negative findings, exemplified by the summary reporting on occupational ETS exposure in the papers by Stockwell et al. (3) and Brownson et al. (5). Hence, unless the underlying data are provided, the Stockwell and Brownson studies are unlikely to be included in any future meta-analysis of occupational ETS exposure and lung cancer. Yet such data clearly would drive down the summary relative risk ratio for such occupational studies.

AGGREGATION BIASES

Published studies involve hidden choices with regard to levels of aggregation or grouping. Typically, the raw data are far more detailed than what is reported with regard to demographic variables, exposure, and environmental variables, for example. Unless the researchers state clearly in advance of the data collection exactly how they will report results, there is a real possibility that groupings may be chosen which exhibit positive findings. For example, a positive finding based on aggregate exposure may be followed by a breakdown according to selected exposure categories only when a dose-response relationship is indicated. EPA failed to confront this problem.

THE EPA IGNORED THE DOSE-RESPONSE MODELING BIAS

There is a modeling bias in the choice of a dose-response relationship and its extrapolation to low-exposure population groups. This modeling bias is perhaps the most controversial and most far-reaching in its effects because a large fraction of the U.S. target population falls into a lower ETS "background" exposure group for which no direct epidemiologic data are available. Of course, a prerequisite for extrapolation to a lower-dose non-spousal exposure is a well-established positive effect for spousal exposure.

Some spousal studies report a dose-response relationship (others do not) but typically it is only the highest spousal exposures which show statistically significant relative risks, with non-significant findings at lower levels of spousal exposure. The attendant large uncertainties associated with dose-response modeling have not been taken into account in the final EPA risk estimates. Those estimates thus are far less certain than EPA claims.

EPA'S RISK ESTIMATE IS HIGHLY LEVERAGED

The epidemiologic data bear directly only on female spousal exposure to ETS. EPA's estimated ETS-attributable annual number of deaths from lung cancer (lcd's) for this group is 470 out of the total estimate of 3,060 lcd's for all U.S. non-smokers and former-smokers, or about 15%. The remaining 2,590 lcd's are obtained through a series of extrapolations: extrapolation of exposure estimates, extrapolation of dose-response functions, extrapolation from non-smokers to former-smokers and the partitioning of smoking-related and non-smoking-related lcd's among former smokers, extrapolation from women to men, etc. Fully 72% of all lcd's are assigned to background exposure. Given this sequence of questionable extrapolations, to characterize the confidence in this estimate as "medium to high" seems strange indeed. Even

the spousal exposure part of the estimate is highly uncertain and is based on an incomplete and questionable meta-analysis.

CONCLUSIONS

A full accounting of all the uncertainty involved in a risk assessment of ETS exposure and lung cancer based on the currently available epidemiologic data could not reasonably exclude zero as an estimate of the number of ETS-attributable deaths in the plausible range of possibilities. In other words, at this stage it is not possible to conclude with confidence that ETS exposure is associated with any increase in lung cancer deaths.

The reported lung cancer risk estimate attributable to ETS is small in relation to the multiple sources of bias. Moreover, in the results reported from individual spousal exposure studies and in the method of combining these results, these small and uncertain risk numbers become highly leveraged when they are applied to the whole U.S. population in order to arrive at the estimate of 3,060 lung cancer deaths supposedly attributable to ETS.

To try to estimate small excess risk numbers for ETS is indeed heroic, but unjustified in face of the myriad sources of bias and confounding and the imprecision of the

exposure measurement. Furthermore, the statistical precision of estimated quantities has been grossly overstated and is derived entirely from the internal precision of the contributing studies. Imprecision derived from extrapolation both to other population groups as well to lower background levels of exposure is not specifically incorporated in uncertainty estimates, and this omission conveys a sense of spurious precision.

Credible risk estimates must be based on better articulation of ETS exposure. To this end, we need better information on population activity patterns and ETS concentrations in different micro-environments. Finally, some important sources of bias can be reduced through advance publication and discussion of the design, analysis, and reporting protocols for all epidemiologic studies -- before data are available.

From the public policy perspective, it seems to me difficult to justify far-reaching policy for highly aggregated and heterogeneous exposure groups for whom ETS effects have not been demonstrated. In the end we will need to depend on sound epidemiologic evidence for public policy decisions, since theoretical arguments of biological plausibility or toxicological extrapolation must remain conjectural. Without reliable information, the attempt to leverage small effects

inconsistently observed in special subpopulations to the entire U.S. target population will never be scientifically convincing.

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